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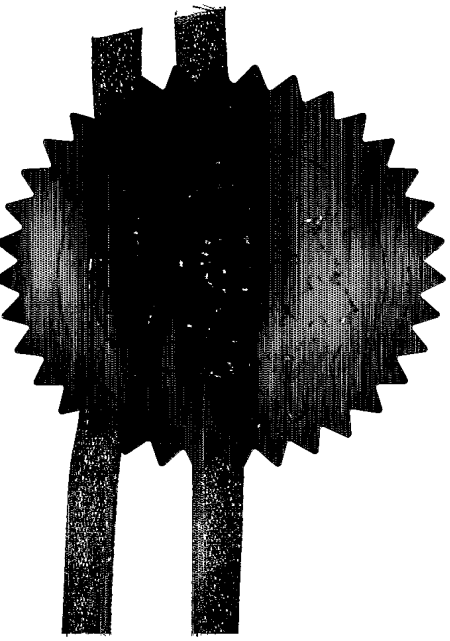

Signed

Dated 13 January 2005

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Patents Form 1/77

Patents Act 1977
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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
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South Wales
NP10 8QQ

1. Your reference 101379-1

2. Patent application number
(The Patent Office will fill in this part) 0403593.7

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
SE-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)* 07822448003

If the applicant is a corporate body, give the country/state of its incorporation Sweden

4. Title of the invention

COMPOUNDS

5. Name of your agent *(if you have one)* Thomas Kerr MILLER

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca
Global Intellectual Property
P O Box 272
Mereside, Alderley Park
Macclesfield,
Cheshire SK10 4GR

Patents ADP number *(if you know it)* 08179707001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	79
Claim *(s)*	5
Abstract	0
Drawing *(s)*	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 17/02/2004

12. Name and daytime telephone number of person to contact in the United Kingdom: Shirley Douglas - 01625 510057

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Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.

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COMPOUNDS

The present invention relates to a group of benzoyl amino heterocyclyl compounds which are useful in the treatment or prevention of a disease or medical condition mediated through glucokinase (GLK), leading to a decreased glucose threshold for insulin secretion. In addition the compounds are predicted to lower blood glucose by increasing hepatic glucose uptake. Such compounds may have utility in the treatment of Type 2 diabetes and obesity. The invention also relates to pharmaceutical compositions comprising said compounds and to methods of treatment of diseases mediated by GLK using said compounds.

In the pancreatic β-cell and liver parenchymal cells the main plasma membrane glucose transporter is GLUT2. Under physiological glucose concentrations the rate at which GLUT2 transports glucose across the membrane is not rate limiting to the overall rate of glucose uptake in these cells. The rate of glucose uptake is limited by the rate of phosphorylation of glucose to glucose-6-phosphate (G-6-P) which is catalysed by glucokinase (GLK) [1]. GLK has a high (6-10mM) Km for glucose and is not inhibited by physiological concentrations of G-6-P [1]. GLK expression is limited to a few tissues and cell types, most notably pancreatic β-cells and liver cells (hepatocytes) [1]. In these cells GLK activity is rate limiting for glucose utilisation and therefore regulates the extent of glucose induced insulin secretion and hepatic glycogen synthesis. These processes are critical in the maintenance of whole body glucose homeostasis and both are dysfunctional in diabetes [2].

In one sub-type of diabetes, Type 2 maturity-onset diabetes of the young (MODY-2), the diabetes is caused by GLK loss of function mutations [3, 4]. Hyperglycaemia in MODY-2 patients results from defective glucose utilisation in both the pancreas and liver [5]. Defective glucose utilisation in the pancreas of MODY-2 patients results in a raised threshold for glucose stimulated insulin secretion. Conversely, rare activating mutations of GLK reduce this threshold resulting in familial hyperinsulinism [6, 7]. In addition to the reduced GLK activity observed in MODY-2 diabetics, hepatic glucokinase activity is also decreased in type 2 diabetics [8]. Importantly, global or liver selective overexpression of GLK prevents or reverses the development of the diabetic phenotype in both dietary and genetic models of the disease [9-12]. Moreover, acute treatment of type 2 diabetics with fructose improves glucose tolerance through stimulation of hepatic glucose utilisation [13]. This effect is believed to be

mediated through a fructose induced increase in cytosolic GLK activity in the hepatocyte by the mechanism described below [13].

Hepatic GLK activity is inhibited through association with GLK regulatory protein (GLKRP). The GLK/GLKRP complex is stabilised by fructose-6-phosphate (F6P) binding to the GLKRP and destabilised by displacement of this sugar phosphate by fructose-1-phosphate (F1P). F1P is generated by fructokinase mediated phosphorylation of dietary fructose. Consequently, GLK/GLKRP complex integrity and hepatic GLK activity is regulated in a nutritionally dependent manner as F6P is elevated in the post-absorptive state whereas F1P predominates in the post-prandial state. In contrast to the hepatocyte, the pancreatic β-cell expresses GLK in the absence of GLKRP. Therefore, β-cell GLK activity is regulated exclusively by the availability of its substrate, glucose. Small molecules may activate GLK either directly or through destabilising the GLK/GLKRP complex. The former class of compounds are predicted to stimulate glucose utilisation in both the liver and the pancreas whereas the latter are predicted to act exclusively in the liver. However, compounds with either profile are predicted to be of therapeutic benefit in treating Type 2 diabetes as this disease is characterised by defective glucose utilisation in both tissues.

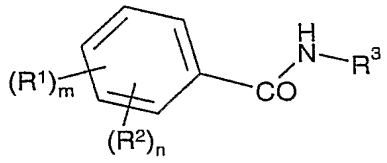
GLK and GLKRP and the K_{ATP} channel are expressed in neurones of the hypothalamus, a region of the brain that is important in the regulation of energy balance and the control of food intake [14-18]. These neurones have been shown to express orectic and anorectic neuropeptides [15, 19, 20] and have been assumed to be the glucose-sensing neurones within the hypothalamus that are either inhibited or excited by changes in ambient glucose concentrations [17, 19, 21, 22]. The ability of these neurones to sense changes in glucose levels is defective in a variety of genetic and experimentally induced models of obesity [23-28]. Intracerebroventricular (icv) infusion of glucose analogues, that are competitive inhibitors of glucokinase, stimulate food intake in lean rats [29, 30]. In contrast, icv infusion of glucose suppresses feeding [31]. Thus, small molecule activators of GLK may decrease food intake and weight gain through central effects on GLK. Therefore, GLK activators may be of therapeutic use in treating eating disorders, including obesity, in addition to diabetes. The hypothalamic effects will be additive or synergistic to the effects of the same compounds acting in the liver and/or pancreas in normalising glucose homeostasis, for the treatment of Type 2 diabetes. Thus the GLK/GLKRP system can be described as a potential "Diabesity" target (of benefit in both Diabetes and Obesity).

In WO0058293 and WO01/44216 (Roche), a series of benzylcarbamoyl compounds are described as glucokinase activators. The mechanism by which such compounds activate GLK is assessed by measuring the direct effect of such compounds in an assay in which GLK activity is linked to NADH production, which in turn is measured optically - see details of the *in vitro* assay described hereinafter. Compounds of the present invention may activate GLK directly or may activate GLK by inhibiting the interaction of GLKRP with GLK.

Further GLK activators have been described in WO03/095438 (substituted phenylacetamides, Roche), WO03/055482 (carboxamide and sulphonamide derivatives, Novo Nordisk), WO2004/002481 (arylcarbonyl derivatives, Novo Nordisk), and in WO03/080585 (amino-substituted benzoylaminoheterocycles, Banyu).

Our International application Number: WO03/000267 describes a group of benzoyl amino pyridyl carboxylic acids which are activators of the enzyme glucokinase (GLK).

Our International application Number: WO03/015774 describes compounds of the Formula (A):

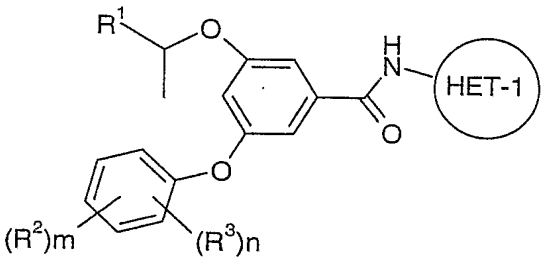


(A)

wherein R^3 is a substituted heterocycle, and wherein the substituents R^1, R^2 and those on the heterocycle R^3 are selected such that the compounds are overall neutral.

We have surprisingly found a small group of compounds, generally a selected subgroup of those described in WO 03/015774, which have generally superior potency for the GLK enzyme, and more advantageous physical properties, including, for example, higher aqueous solubility, higher permeability, and/or lower plasma protein binding. Consequently, such compounds would be expected to display higher plasma free drug levels and superior in vivo efficacy after oral dosing as determined, for example, by activity in Oral Glucose Tolerance Tests (OGTTs). Therefore this group of compounds would be expected to provide superior oral exposure at a lower dose and thereby be particularly suitable for use in the treatment or prevention of a disease or medical condition mediated through GLK.

Thus, according to the first aspect of the invention there is provided a compound of Formula (I):



(I)

wherein:

R^1 is methoxymethyl;

R^2 is selected from $-C(O)NR^4R^5$, $-SO_2NR^4R^5$, $-S(O)_pR^4$ and HET-2;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^6;

HET-2 is a 4-, 5- or 6-membered, C- or N-linked heterocyclyl ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- , and wherein a sulphur atom in the heterocyclic ring may optionally be oxidised to a S(O) or $S(O)_2$ group, which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^7;

R^3 is selected from halo, fluoromethyl, difluoromethyl, trifluoromethyl, methyl, methoxy and cyano;

R^4 is selected from hydrogen, (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$] and HET-2;

R^5 is hydrogen or (1-4C)alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached may form a 4-6 membered heterocyclyl ring system as defined by HET-3;

R^6 is independently selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl and HET-4;

R^7 is selected from $-OR^5$, (1-4C)alkyl, -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-3 is an N-linked, 4 to 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8;

R^8 is selected from $-OR^5$, (1-4C)alkyl, -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkylamino, di(1-4C)alkylamino, HET-3 (wherein said ring is unsubstituted), (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-4 is a 5- or 6-membered, C-or N- linked unsubstituted heteroaryl ring containing 1, 2 or 3 ring heteroatoms independently selected from O, N and S;

p is (independently at each occurrence) 0, 1 or 2;

m is 0 or 1;

n is 0, 1 or 2;

provided that when m is 0, then n is 1 or 2;

or a salt, pro-drug or solvate thereof.

It will be understood that when R^4 is $-C(O)NR^5R^5$, each R^5 is independently selected from hydrogen and (1-4C)alkyl, and therefore this definition of R^4 includes (but is not limited to) $-CONH_2$, -CONHMe, $-CONMe_2$ and –CONMeEt.

It will be understood that where a compound of the formula (I) contains more than one HET-2 ring, they may be the same or different.

It will be understood that where a compound of the formula (I) contains more than one group R^4, they may be the same or different.

It will be understood that where a compound of the formula (I) contains more than one group R^5, they may be the same or different.

It will be understood that where a compound of the formula (I) contains more than one group R^8, they may be the same or different.

A similar convention applies for all other groups and substituents on a compound of formula (I) as hereinbefore defined.

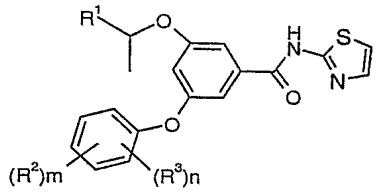
Compounds of Formula (I) may form salts which are within the ambit of the invention. Pharmaceutically acceptable salts are preferred although other salts may be useful in, for example, isolating or purifying compounds.

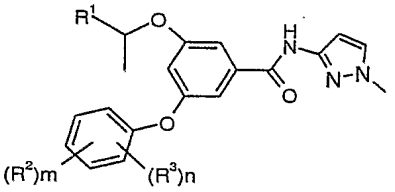
In another aspect, the invention relates to compounds of formula (I) as hereinabove defined or to a pharmaceutically acceptable salt.

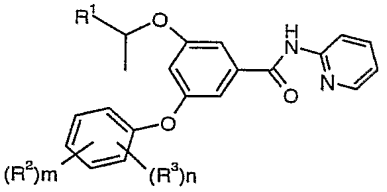
In another aspect, the invention relates to compounds of formula (I) as hereinabove defined or to a pro-drug thereof. Suitable examples of pro-drugs of compounds of formula (I) are in-vivo hydrolysable esters of compounds of formula (I). Therefore in another aspect, the invention relates to compounds of formula (I) as hereinabove defined or to an in-vivo hydrolysable ester thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched-chain alkyl groups such as *t*-butyl are specific for the branched chain version only. For example, "(1-4C)alkyl" includes methyl, ethyl, propyl, isopropyl and *t*-butyl. An analogous convention applies to other generic terms.

For the avoidance of doubt, reference to the group HET-1 containing a nitrogen in the 2-position, is intended to refer to the 2-position relative to the amide nitrogen atom to which the group is attached. For example, the following structures are encompassed (but not limited to):







Suitable examples of HET-1 as a 5- or 6-membered, C-linked heteroaryl ring as hereinbefore defined, include thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl and triazolyl.

It will be understood that HET-2 can be a saturated, or partially or fully unsaturated ring.

Suitable examples of HET-2 include azetidinyl, furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, morpholino, morpholinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-

dioxotetrahydrothienyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, 2-oxo-1,3,4-(4-triazolinyl), 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 1,2,4-triazolyl, 1,2,3-triazolyl, pyranyl, and 4-pyridonyl.

It will be understood that HET-2 may be linked by any appropriate available C or N atom, therefore for example, for HET-2 as "imidazolyl" includes 1- , 2-, 4- and 5- imidazolyl.

Suitable examples of HET-3 are morpholino, piperidinyl, piperazinyl, pyrrolidinyl and azetidinyl.

Suitable examples of HET-4 are furyl, pyrrolyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl and triazolyl.

It will be appreciated that, where definitions of heterocylyl groups HET-1 to HET-4 encompass heteroaryl rings which may be substituted on nitrogen, such substitution may not result in charged quaternary nitrogen atoms. It will be appreciated that the definitions of HET-1 to HET-4 are not intended to include any O-O, O-S or S-S bonds. It will be appreciated that the definitions of HET-1 to HET-4 are not intended to include unstable structures.

Examples of **(1-4C)alkyl** include methyl, ethyl, propyl, isopropyl, butyl and tert-butyl; examples of **(3-6C)cycloalkyl** include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; examples of **halo** include fluoro, chloro, bromo and iodo; examples of **hydroxy(1-4C)alkyl** include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-hydroxyisopropyl and 4-hydroxybutyl; examples of **(1-4C)alkoxy(1-4C)alkyl** include methoxymethyl, ethoxymethyl, tert-butoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, methoxypropyl, 2-methoxypropyl and methoxybutyl; examples of **(1-4C)alkylS(O)p(1-4C)alkyl** include methylsulfinylmethyl, ethylsulfinylmethyl, ethylsulfinylethyl, methylsulfinylpropyl, methylsulfinylbutyl, methylsulfonylmethyl, ethylsulfonylmethyl, ethylsulfonylethyl, methylsulfonylpropyl, methylsulfonylbutyl, methylthiomethyl, ethylthiomethyl, ethylthioethyl, methylthiopropyl, and methylthiobutyl; examples of **amino(1-4C)alkyl** include aminomethyl, aminoethyl, 2-aminopropyl, 3-aminopropyl, 1-aminoisopropyl and 4-aminobutyl; examples of **(1-4C)alkylamino(1-4C)alkyl** include (N-methyl)aminomethyl, (N-ethyl)aminomethyl, 1-((N-methyl)amino)ethyl, 2-((N-methyl)amino)ethyl, (N-ethyl)aminoethyl, (N-methyl)aminopropyl, and 4-((N-methyl)amino)butyl; examples of **di(1-4C)alkylamino(1-4C)alkyl** include

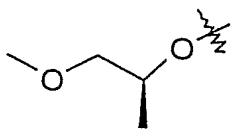
dimethylaminomethyl, methyl(ethyl)aminomethyl, methyl(ethyl)aminoethyl, (N,N-diethyl)aminoethyl, (N,N-dimethyl)aminopropyl and (N,N-dimethyl)aminobutyl; examples of **(1-4C)alkylamino** include methylamino, ethylamino, propylamino, isopropylamino, butylamino and tert-butylamino; examples of **di(1-4C)alkylamino** include dimethylamino, methyl(ethyl)amino, diethylamino, dipropylamino, di-isopropylamino and dibutylamino; examples of **–C(O)(1-4C)alkyl** include methylcarbonyl, ethylcarbonyl, propylcarbonyl and tert-butyl carbonyl.

It is to be understood that, insofar as certain of the compounds of Formula (I) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of stimulating GLK directly or inhibiting the GLK/GLKRP interaction. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. It is also to be understood that certain compounds may exist in tautomeric forms and that the invention also relates to any and all tautomeric forms of the compounds of the invention which activate GLK.

In one embodiment of the invention are provided compounds of formula (I), in an alternative embodiment are provided pharmaceutically-acceptable salts of compounds of formula (I), in a further alternative embodiment are provided in-vivo hydrolysable esters of compounds of formula (I), and in a further alternative embodiment are provided pharmaceutically-acceptable salts of in-vivo hydrolysable esters of compounds of formula (I).

Preferred values of each variable group are as follows. Such values may be used where appropriate with any of the values, definitions, claims, aspects or embodiments defined hereinbefore or hereinafter.

(1) R^1 is methoxymethyl and the configuration is preferably (S), that is:



(2) R^2 is $-C(O)NR^4R^5$

(3) R^2 is $-SO_2NR^4R^5$

(4) R^2 is $-S(O)_pR^4$

(5) R^2 is HET-2

(6) m is 1 and R^2 is in the para position relative to the ether linkage

(7) m is 1 and n is 0 or 1

(8) m is 1 and n is 0

(9) m is 1, n is 0 and R^2 is in the para position relative to the ether linkage

(10) n is 0

(11) n is 1

(12) n is 2

(13) n is 2 and both R^3 are halo

(14) R^3 is halo or trifluoromethyl

(15) R^3 is halo

(16) R^3 is chloro or fluoro

(17) R^3 is fluoro

(18) n is 2 and both R^3 are fluoro,

(19) n is 2, both R^3 are fluoro and are in the 3- and 5-positions relative to the ether linkage

(20) p is 0

(21) p is 1

(22) p is 2

(23) HET-1 is a 5-membered heteroaryl ring

(24) HET-1 is a 6-membered heteroaryl ring

(25) HET-1 is substituted with 1 or 2 substituents independently selected from R^6

(26) HET-1 is substituted with 1 substituent selected from R^6

(27) HET-1 is unsubstituted

(28) HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, and triazolyl

(29) HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl

(30) HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl

(31) HET-1 is selected from thiazolyl, pyrazolyl and oxazolyl

(32) HET-1 is selected from thiadiazolyl and oxadiazolyl

(33) HET-1 is selected from 1,3,4-thiadiazolyl and 1,3,4-oxadiazolyl

(34) HET-1 is selected from 1,2,4-oxadiazolyl and 1,2,4-oxadiazolyl

(35) HET-1 is pyridyl

(36) HET-1 is pyrazinyl

(37) R^6 is selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl and HET-4

(38) R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, dimethylaminomethyl

(39) R^6 is selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, and di(1-4C)alkylamino(1-4C)alkyl

(40) R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl

(41) R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl and methoxymethyl

(42) R^6 is selected from methyl, ethyl, bromo, chloro and fluoro

(43) R^6 is methyl

(44) when 2 substituents R^6 are present, both are selected from methyl, ethyl, bromo, chloro and fluoro

(45) when 2 substituents R^6 are present, both are methyl

(46) HET-4 is selected from furyl, pyrrolyl and thienyl

(47) HET-4 is furyl

(48) R^4 is hydrogen

(49) R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$]

(50) R^4 is (1-4C)alkyl [optionally substituted by 1 substituent selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl and $-C(O)NR^5R^5$]

(51) R^4 is HET-2

(52) R^4 is selected from hydrogen, (1-4C)alkyl, and (1-4C)alkyl substituted with $-OR^5$

(53) HET-2 is unsubstituted

(54) HET-2 is substituted with 1 or 2 substituents independently selected from (1-4C)alkyl, hydroxy and (1-4C)alkoxy

(55) HET-2 is a fully saturated ring system

(56) HET-2 is a fully unsaturated ring system

(57) HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl

(58) HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, pyrrolidinyl, thiomorpholinyl, tetrahydrofuranyl, and tetrahydropyranyl

(59) HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl

(60) HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, pyrrolidinyl, pyrrolidonyl, 2-oxazolidinonyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxotetrahydrothienyl, and 2-oxoimidazolidinyl

(61) HET-2 is selected from morpholino, furyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, pyrrolidinyl, 2-pyrrolidonyl, 2-oxazolidinonyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxotetrahydrothienyl, and 2-oxoimidazolidinyl

(62) HET-2 is selected from morpholino, furyl, imidazolyl, isoxazolyl, oxadiazolyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, pyrrolidinyl, 2-pyrrolidonyl, tetrahydropyranyl, 1,1-dioxotetrahydrothienyl, and 2-oxoimidazolidinyl

(63) R^5 is hydrogen

(64) R^5 is (1-4)alkyl

(65) R^5 is hydrogen or methyl

(66) R^7 is selected from $-OR^5$, (1-4C)alkyl, -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkoxy(1-4C)alkyl, and hydroxy(1-4C)alkyl

(67) R^7 is selected from $-OR^5$, (1-4C)alkyl, -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, and hydroxy(1-4C)alkyl

(68) R^7 is selected from hydroxy, methoxy, -COMe, $-CONH_2$, -CONHMe, $-CONMe_2$, and hydroxymethyl

(69) R^7 is selected from (1-4C)alkyl, hydroxy and (1-4C)alkoxy

(70) R^7 is selected from methyl, ethyl, methoxy and hydroxy

(71) R^8 is selected from methyl, hydroxy, methoxy, -COMe, $-CONH_2$, -CONHMe, $-CONMe_2$, hydroxymethyl, hydroxyethyl, -NHMe and $-NMe_2$(72) R^8 is selected from morpholino, piperidinyl, piperazinyl, pyrrolidinyl and azetidinyl

(73) R^8 is selected from methyl, -COMe, $-CONH_2$, hydroxyethyl and hydroxy

(74) HET-3 is a fully saturated ring

(75) HET-3 is selected from morpholino, piperidinyl, piperazinyl, pyrrolidinyl and azetidinyl

(76) R^4 and R^5 together with the nitrogen to which they are attached form a ring as defined by HET-3

According to a further feature of the invention there is provided the following preferred groups of compounds of the invention:

In a futher aspect of the invention there is provided a compound of Formula (I) wherein:

R^1 is methoxymethyl;

R^2 is selected from $-C(O)NR^4R^5$, $-SO_2NR^4R^5$, $-S(O)_pR^4$ and HET-2;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1, 2 or 3 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^6;

HET-2 is a 5- or 6-membered, C- or N-linked heterocyclyl ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- , and wherein a sulphur atom in the heterocyclic ring may optionally be oxidised to an S(O) or $S(O)_2$ group, which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^7;

R^3 is selected from halo, fluoromethyl, difluoromethyl, trifluoromethyl, methyl, methoxy and cyano;

R^4 is selected from hydrogen, (1-4C)alkyl, [optionally substituted by $-OR^5$] and HET-2;

R^5 is hydrogen or (1-4C)alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached may form a 4-6 membered heterocyclyl ring system as defined by HET-3;

R^6 is independently selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl and HET-4;

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

HET-3 is an N-linked, 4 to 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to an S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8;

R^8 is selected from $-OR^5$ and (1-4C)alkyl;

HET-4 is a 5- or 6-membered, C-or N- linked unsubstituted heteroaryl ring containing 1, 2 or 3 ring heteroatoms independently selected from O, N and S;

p is (independently at each occurrence) 0, 1 or 2;

m is 0 or 1;

n is 0, 1 or 2;

provided that when m is 0, then n is 1 or 2;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein:

R^1 is methoxymethyl;

R^2 is selected from $-C(O)NR^4R^5$, $-SO_2NR^4R^5$, $-S(O)_pR^4$ and HET-2;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^6;

HET-2 is a 4-, 5- or 6-membered, C- or N-linked heterocyclyl ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- , and wherein a sulphur atom in the heterocyclic ring may optionally be oxidised to an S(O) or $S(O)_2$ group, which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^7;

R^3 is selected from halo, fluoromethyl, difluoromethyl, trifluoromethyl, methyl, methoxy and cyano;

R^4 is selected from (1-4C)alkyl [substituted by 1 or 2 substituents independently selected from HET-2, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$];

R^5 is hydrogen or (1-4C)alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached may form a 4-6 membered heterocyclyl ring system as defined by HET-3;

R^6 is independently selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl and HET-4;

R^7 is selected from $-C(O)$(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-3 is an N-linked, 4 to 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to an S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8;

R^8 is selected from $-C(O)$(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkylamino, di(1-4C)alkylamino, HET-3 (wherein said ring is unsubstituted), (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-4 is a 5- or 6-membered, C-or N- linked unsubstituted heteroaryl ring containing 1, 2 or 3 ring heteroatoms independently selected from O, N and S;

p is (independently at each occurrence) 0, 1 or 2;

m is 0 or 1;

n is 0, 1 or 2;

provided that when m is 0, then n is 1 or 2;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is a 5- or 6-membered heteroaryl ring;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$];

$R^5$is hydrogen or methyl;

HET-2 is a 5- or 6- membered heterocyclyl ring as hereinbefore defined, containing 1 or 2 heteroatoms independently selected from O, N and S; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is a 5- or 6-membered heteroaryl ring;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$];

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is a 5- or 6- membered heterocyclyl ring as hereinbefore defined, containing 1 or 2 heteroatoms independently selected from O, N and S; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl and $-C(O)NR^5R^5$];

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl and $-C(O)NR^5R^5$];

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-

dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl and $-C(O)NR^5R^5$];

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl and $-C(O)NR^5R^5$];

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is selected from hydrogen, (1-4C)alkyl, [optionally substituted by $-OR^5$] and HET-2;

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from morpholino, furyl, imidazolyl, isoxazolyl, oxadiazolyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, pyrrolidinyl, 2-pyrrolidonyl, tetrahydropyranyl, 1,1-dioxotetrahydrothienyl, and 2-oxoimidazolidinyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl and pyridazinyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is selected from hydrogen, (1-4C)alkyl, [optionally substituted by $-OR^5$] and HET-2;

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from morpholino, furyl, imidazolyl, isoxazolyl, oxadiazolyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, pyrrolidinyl, 2-pyrrolidonyl, tetrahydropyranyl, 1,1-dioxotetrahydrothienyl, and 2-oxoimidazolidinyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is selected from (1-4C)alkyl, [optionally substituted by $-OR^5$] and HET-2;

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from piperidinyl, piperazinyl, 3-oxopiperazinyl, 2-pyrrolidonyl, 2,5-dioxopyrrolidinyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 2-oxoimidazolidinyl, and 2,4-dioxoimidazolidinyl; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is selected from (1-4C)alkyl, [optionally substituted by $-OR^5$] and HET-2;

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is piperidinyl or piperazinyl; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 ;

HET-1 is selected from thiazolyl, thiadiazolyl and pyrazolyl;

R^2 is $-CONR^4R^5$;

R^4 is piperidinyl or piperazinyl, optionally substituted with methyl;

$R^5$is hydrogen or methyl;

R^6 is methyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl and pyridazinyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is selected from (1-4C)alkyl, [optionally substituted by $-OR^5$] and HET-2;

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from piperidinyl, piperazinyl, 3-oxopiperazinyl, 2-pyrrolidonyl, 2,5-dioxopyrrolidinyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 2-oxoimidazolidinyl, and 2,4-dioxoimidazolidinyl; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl and pyridazinyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is selected from (1-4C)alkyl, [optionally substituted by $-OR^5$] and HET-2;

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is piperidinyl or piperazinyl; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 and R^5 together with the nitrogen to which they are attached form a morpholino, piperidinyl, piperazinyl, pyrrolidinyl or azetidinyl ring, which ring is optionally substituted on a carbon or nitrogen atom by (1-4C)alkyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from morpholino, furyl, imidazolyl, isoxazolyl, oxadiazolyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, pyrrolidinyl, 2-pyrrolidonyl, tetrahydropyranyl, 1,1-dioxotetrahydrothienyl, and 2-oxoimidazolidinyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl and pyridazinyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 and R^5 together with the nitrogen to which they are attached form a morpholino, piperidinyl, piperazinyl, pyrrolidinyl or azetidinyl ring, which ring is optionally substituted on a carbon or nitrogen atom by (1-4C)alkyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from morpholino, furyl, imidazolyl, isoxazolyl, oxadiazolyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, pyrrolidinyl, 2-pyrrolidonyl, tetrahydropyranyl, 1,1-dioxotetrahydrothienyl, and 2-oxoimidazolidinyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0;

HET-1 is selected from thiazolyl, thiadiazolyl and pyrazolyl;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together with the nitrogen to which they are attached form a piperidinyl, or piperazinyl ring, which ring is optionally substituted on a carbon or nitrogen atom by (1-4C)alkyl or by a pyrrolidinyl ring;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is a 5- or 6-membered heteroaryl ring;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$];

$R^5$is hydrogen or methyl;

HET-2 is a 5- or 6- membered heterocyclyl ring as hereinbefore defined, containing 1 or 2 heteroatoms independently selected from O, N and S; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is a 5- or 6-membered heteroaryl ring;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$];

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is a 5- or 6- membered heterocyclyl ring as hereinbefore defined, containing 1 or 2 heteroatoms independently selected from O, N and S; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl and $-C(O)NR^5R^5$];

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is selected from hydrogen, (1-4C)alkyl, [optionally substituted by $-OR^5$] and HET-2;

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl and $-C(O)NR^5R^5$];

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is selected from hydrogen, (1-4C)alkyl, [optionally substituted by $-OR^5$] and HET-2;

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0;

HET-1 is selected from thiazolyl, thiadiazolyl and pyrazolyl;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^4 is (1-4C)alkyl;

R^6 is methyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is a 5- or 6-membered heteroaryl ring;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^5 is hydrogen or (1-4C)alkyl;

HET-2 is a 5- or 6- membered heterocyclyl ring as hereinbefore defined, containing 1 or 2 heteroatoms independently selected from O, N and S; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^5 is hydrogen or methyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^5 is hydrogen or methyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^5 is hydrogen or methyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^5 is hydrogen or methyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methoxymethyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

Further preferred compounds of the invention are each of the Examples, each of which provides a further independent aspect of the invention. In further aspects, the present invention also comprises any two or more compounds of the Examples.

In one aspect, particular compounds of the invention comprise any one or more of:

3-[(1S)-2-methoxy-(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)-5-[4-(methylsulfonyl)phenoxy]benzamide;

3-[(1S)-2-methoxy-(1-methylethyl)oxy]-5-[4-(methylsulfonyl)phenoxy]-N-1,3-thiazol-2-ylbenzamide;

3-[(1S)-2-methoxy-(1-methylethyl)oxy]-5-[4-(methylsulfonyl)phenoxy]-N-(4-methyl-1,3-thiazol-2-yl)benzamide;

3-[(1S)-2-methoxy-(1-methylethyl)oxy]-5-[4-(methylsulfonyl)phenoxy]-N-(5-methyl-1,3-thiazol-2-yl)benzamide;

3-[(1S)-2-methoxy-(1-methylethyl)oxy]-5-[4-(methylsulfonyl)phenoxy]-N-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide;

3-[(1S)-2-methoxy-(1-methylethyl)oxy]-5-(4-{[(1-methylpiperidin-4-yl)amino]carbonyl}phenoxy)-N-1,3-thiazol-2-ylbenzamide;

3-[(1S)-2-methoxy-(1-methylethyl)oxy]-5-{4-[(4-methylpiperazin-1-yl)carbonyl]phenoxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide; and

3-[(1S)-2-methoxy-(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)-5-[3-(methylsulfinyl)phenoxy]benzamide;

or a salt, pro-drug or solvate thereof.

The compounds of the invention may be administered in the form of a pro-drug. A pro-drug is a bioprecursor or pharmaceutically acceptable compound being degradable in

the body to produce a compound of the invention (such as an ester or amide of a compound of the invention, particularly an in-vivo hydrolysable ester). Various forms of prodrugs are known in the art. For examples of such prodrug derivatives, see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen;

c) H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

e) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and

f) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

The contents of the above cited documents are incorporated herein by reference.

Examples of pro-drugs are as follows. An in-vivo hydrolysable ester of a compound of the invention containing a carboxy or a hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include C_1 to C_6alkoxymethyl esters for example methoxymethyl, C_1 to C_6alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_3 to C_8cycloalkoxycarbonyloxyC_1 to C_6alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters.

An in-vivo hydrolysable ester of a compound of the invention containing a hydroxy group includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

A suitable pharmaceutically-acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for

example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of a benzoxazinone derivative of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

A further feature of the invention is a pharmaceutical composition comprising a compound of Formula (I) as defined above, or a salt, solvate or prodrug thereof, together with a pharmaceutically-acceptable diluent or carrier.

According to another aspect of the invention there is provided a compound of Formula (I) as defined above for use as a medicament.

Further according to the invention there is provided a compound of Formula (I) for use in the preparation of a medicament for treatment of a disease mediated through GLK, in particular type 2 diabetes.

The compound is suitably formulated as a pharmaceutical composition for use in this way.

According to another aspect of the present invention there is provided a method of treating GLK mediated diseases, especially diabetes, by administering an effective amount of a compound of Formula (I) or salt, solvate or pro-drug thereof, to a mammal in need of such treatment.

Specific diseases which may be treated by a compound or composition of the invention include: blood glucose lowering in Diabetes Mellitus type 2 without a serious risk of hypoglycaemia (and potential to treat type 1), dyslipidemia, obesity, insulin resistance, metabolic syndrome X, impaired glucose tolerance.

As discussed above, thus the GLK/GLKRP system can be described as a potential "Diabesity" target (of benefit in both Diabetes and Obesity). Thus, according to another aspect of the invention there if provided the use of a compound of Formula (I) or salt, solvate or pro-drug thereof, in the preparation of a medicament for use in the combined treatment or prevention of diabetes and obesity.

According to another aspect of the invention there if provided the use of a compound of Formula (I) or salt, solvate or pro-drug thereof, in the preparation of a medicament for use in the treatment or prevention of obesity.

According to a further aspect of the invention there is provided a method for the combined treatment of obesity and diabetes by administering an effective amount of a compound of Formula (I) or salt, solvate or pro-drug thereof, to a mammal in need of such treatment.

According to a further aspect of the invention there is provided a method for the treatment of obesity by administering an effective amount of a compound of Formula (I) or salt, solvate or pro-drug thereof, to a mammal in need of such treatment.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium

phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum

tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula (I) will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula (I) for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

The elevation of GLK activity described herein may be applied as a sole therapy or in combination with one or more other substances and/or treatments for the indicated being treated. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Simultaneous treatment may be in a single tablet or in separate tablets. For example in the treatment of diabetes mellitus, chemotherapy may include the following main categories of treatment:

1) Insulin and insulin analogues;
2) Insulin secretagogues including sulphonylureas (for example glibenclamide, glipizide) and prandial glucose regulators (for example repaglinide, nateglinide);
3) Insulin sensitising agents including PPARγ agonists (for example pioglitazone and rosiglitazone);
4) Agents that suppress hepatic glucose output (for example metformin).
5) Agents designed to reduce the absorption of glucose from the intestine (for example acarbose);
6) Agents designed to treat the complications of prolonged hyperglycaemia;
7) Anti-obesity agents (for example sibutramine and orlistat);
8) Anti- dyslipidaemia agents such as, HMG-CoA reductase inhibitors (statins, eg rosuvastatin, pravastatin); PPARα agonists (fibrates, eg gemfibrozil); bile acid sequestrants (cholestyramine); cholesterol absorption inhibitors (plant stanols,

synthetic inhibitors); bile acid absorption inhibitors (IBATi) and nicotinic acid and analogues (niacin and slow release formulations);

9) Antihypertensive agents such as, β blockers (eg atenolol, metoprolol, inderal); ACE inhibitors (eg lisinopril); Calcium antagonists (eg. nifedipine); Angiotensin receptor antagonists (eg candesartan), α antagonists and diuretic agents (eg. furosemide, benzthiazide);

10) Haemostasis modulators such as, antithrombotics, activators of fibrinolysis and antiplatelet agents; thrombin antagonists; factor Xa inhibitors; factor VIIa inhibitors); antiplatelet agents (eg. aspirin, clopidogrel); anticoagulants (heparin and Low molecular weight analogues, hirudin) and warfarin; and

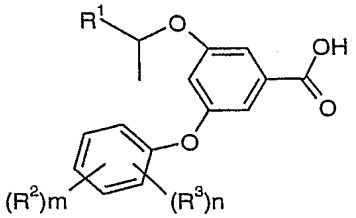
11) Anti-inflammatory agents, such as non-steroidal anti-infammatory drugs (eg. aspirin) and steroidal anti-inflammatory agents (eg. cortisone).

According to another aspect of the present invention there is provided individual compounds produced as end products in the Examples set out below and salts, solvates and pro-drugs thereof.

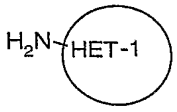
A compound of the invention, or a salt thereof, may be prepared by any process known to be applicable to the preparation of such compounds or structurally related compounds. Functional groups may be protected and deprotected using conventional methods. For examples of protecting groups such as amino and carboxylic acid protecting groups (as well as means of formation and eventual deprotection), see T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", Second Edition, John Wiley & Sons, New York, 1991.

Processes for the synthesis of compounds of Formula (I) are provided as a further feature of the invention. Thus, according to a further aspect of the invention there is provided a process for the preparation of a compound of Formula (I), which comprises:

(a) reaction of an acid of Formula (III) or activated derivative thereof with a compound of Formula (IV),



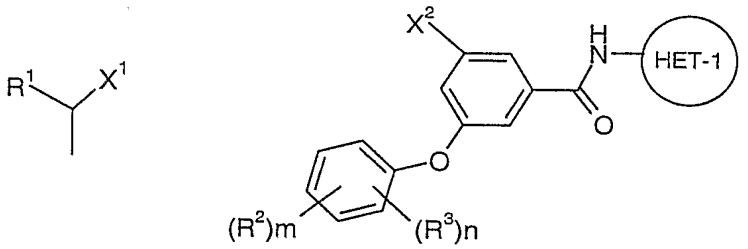
(III)



(IV);

or

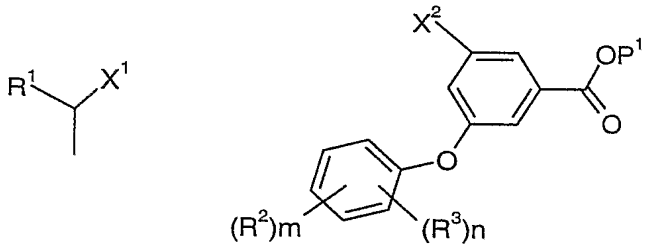
(b) reaction of a compound of Formula (V) with a compound of Formula (VI),



(V) (VI)

wherein X^1 is a leaving group and X^2 is a hydroxyl group or X^1 is a hydroxyl group and X^2 is a leaving group;

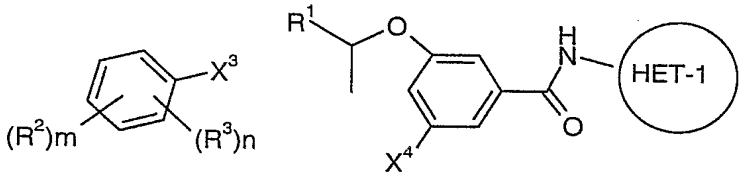
process (b) could also be accomplished using the intermediate ester Formula (VII), wherein P^1 is a protecting group as hereinafter described, followed by ester hydrolysis and amide formation by procedures described elsewhere and well known to those skilled in the art;



(V) (VII)

or

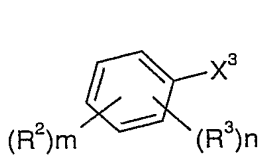
(c) reaction of a compound of Formula (VIII) with a compound of Formula (IX)



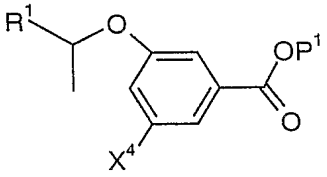
(VIII) (IX)

wherein X^3 is a leaving group or an organometallic reagent and X^4 is a hydroxyl group or X^3 is a hydroxyl group and X^4 is a leaving group or an organometallic reagent;

process (c) could also be accomplished using the intermediate ester Formula (X), followed by ester hydrolysis and amide formation by procedures described elsewhere and well known to those skilled in the art;



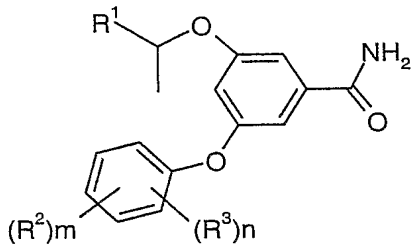
(VIII)



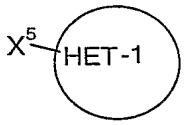
(X)

or

(d) reaction of a compound of Formula (XI) with a compound of Formula (XII),



(XI)



(XII);

wherein X^5 is a leaving group;

and thereafter, if necessary:

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups; and/or

iii) forming a salt, pro-drug or solvate thereof.

Suitable leaving groups X^1 to X^5 for processes b) to d) are any leaving group known in the art for these types of reactions, for example halo, alkoxy, trifluoromethanesulfonyloxy, methanesulfonyloxy, or p-toulenesulfonyloxy; or a group (such as a hydroxy group) that may be converted into a leaving group (such as an oxytriphenylphosphonium group) *in situ*.

Examples of conversions of a compound of Formula (I) into another compound of Formula (I), well known to those skilled in the art, include functional group interconversions such as hydrolysis,oxidation or reduction, and/or further functionalisation by standard reactions such as amide or metal-catalysed coupling, or nucleophilic displacement reactions;

Specific reaction conditions for the above reactions are as follows, wherein when P^1 is a protecting group P^1 is preferably C_{1-4}alkyl, for example methyl or ethyl:

Process a) – coupling reactions of amino groups with carboxylic acids to form an amide are well known in the art. For example,

(i) using an appropriate coupling reaction, such as a carbodiimide coupling reaction performed with EDAC in the presence of DMAP in a suitable solvent such as DCM, chloroform or DMF at room temperature; or

(ii) reaction in which the carboxylic group is activated to an acid chloride by reaction with oxalyl chloride in the presence of a suitable solvent such as methylene chloride. The acid chloride can then be reacted with a compound of Formula (IV) in the presence of a base, such as triethylamine or pyridine, in a suitable solvent such as chloroform or DCM at a temperature between 0°C and room temperature.

Process b) – compounds of Formula (V) and (VI) can be reacted together in a suitable solvent, such as DMF or THF, with a base such as sodium hydride or potassium *tert*-butoxide, at a temperature in the range 0 to 100°C, optionally using metal catalysis such as palladium(II)acetate, palladium on carbon, copper(II)acetate or copper(I)iodide; Alternatively, compounds of Formula (V) and (VI) can be reacted together in a suitable solvent, such as THF or DCM, with a suitable phosphine such as triphenylphosphine, and azodicarboxylate such as diethylazodicarboxylate;

Process c) - compounds of Formula (VIII) and (IX) can be reacted together in a suitable solvent, such as DMF or THF, with a base such as sodium hydride or potassium tert-butoxide, at a temperature in the range 0 to 100°C, optionally using metal catalysis such as palladium(II)acetate, palladium on carbon, copper(II)acetate or copper(I)iodide;

Process d) – reaction of a compound of Formula (XI) with a compound of Formula (XII) can be performed in a polar solvent, such as DMF or a non-polar solvent such as THF with a strong base, such as sodium hydride or potassium *tert*-butoxide at a temperature between 0 and 100°C, optionally using metal catalysis, such as palladium(II)acetate, palladium on carbon, copper(II)acetate or copper(I)iodide.

Certain intermediates of formula (III), (VI), (VII), (IX) and/or (XI) are believed to be novel and comprise an independent aspect of the invention.

Certain intermediates of formula (III), (IX) and/or (XI) wherein R^1 is methoxymethyl are believed to be novel and comprise an independent aspect of the invention.

During the preparation process, it may be advantageous to use a protecting group for a functional group within the molecule. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect

removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower" signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or araliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (e.g. isopropyl, t-butyl); lower alkoxy lower alkyl groups (e.g. methoxymethyl, ethoxymethyl, isobutoxymethyl; lower aliphatic acyloxy lower alkyl groups, (e.g. acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (e.g. 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl groups (e.g. p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (e.g. trimethylsilyl and t-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (e.g. trimethylsilylethyl); and (2-6C)alkenyl groups (e.g. allyl and vinylethyl).

Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, metal- or enzymically-catalysed hydrolysis.

Examples of hydroxy protecting groups include lower alkenyl groups (e.g. allyl); lower alkanoyl groups (e.g. acetyl); lower alkoxycarbonyl groups (e.g. t-butoxycarbonyl); lower alkenyloxycarbonyl groups (e.g. allyloxycarbonyl); aryl lower alkoxycarbonyl groups (e.g. benzoyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl); tri lower alkyl/arylsilyl groups (e.g. trimethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl); aryl lower alkyl groups (e.g. benzyl) groups; and triaryl lower alkyl groups (e.g. triphenylmethyl).

Examples of amino protecting groups include formyl, aralkyl groups (e.g. benzyl and substituted benzyl, e.g. p-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-p-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (e.g. t-butoxycarbonyl); lower alkenyloxycarbonyl (e.g. allyloxycarbonyl); aryl lower alkoxycarbonyl groups (e.g. benzyloxycarbonyl, p-methoxybenzyloxycarbonyl,

o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl; trialkylsilyl (e.g. trimethylsilyl and t-butyldimethylsilyl); alkylidene (e.g. methylidene); benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base, metal- or enzymically-catalysed hydrolysis, or photolytically for groups such as o-nitrobenzyloxycarbonyl, or with fluoride ions for silyl groups.

Examples of protecting groups for amide groups include aralkoxymethyl (e.g. benzyloxymethyl and substituted benzyloxymethyl); alkoxymethyl (e.g. methoxymethyl and trimethylsilylethoxymethyl); tri alkyl/arylsilyl (e.g. trimethylsilyl, t-butyldimethylsily, t-butyldiphenylsilyl); tri alkyl/arylsilyloxymethyl (e.g. t-butyldimethylsilyloxymethyl, t-butyldiphenylsilyloxymethyl); 4-alkoxyphenyl (e.g. 4-methoxyphenyl); 2,4-di(alkoxy)phenyl (e.g. 2,4-dimethoxyphenyl); 4-alkoxybenzyl (e.g. 4-methoxybenzyl); 2,4-di(alkoxy)benzyl (e.g. 2,4-di(methoxy)benzyl); and alk-1-enyl (e.g. allyl, but-1-enyl and substituted vinyl e.g. 2-phenylvinyl).

Aralkoxymethyl, groups may be introduced onto the amide group by reacting the latter group with the appropriate aralkoxymethyl chloride, and removed by catalytic hydrogenation. Alkoxymethyl, tri alkyl/arylsilyl and tri alkyl/silyloxymethyl groups may be introduced by reacting the amide with the appropriate chloride and removing with acid; or in the case of the silyl containing groups, fluoride ions. The alkoxyphenyl and alkoxybenzyl groups are conveniently introduced by arylation or alkylation with an appropriate halide and removed by oxidation with ceric ammonium nitrate. Finally alk-1-enyl groups may be introduced by reacting the amide with the appropriate aldehyde and removed with acid.

The following examples are for illustration purposes and are not intended to limit the scope of this application. Each exemplified compound represents a particular and independent aspect of the invention. In the following non-limiting Examples, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation in *vacuo* and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at room temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;

(iii) yields are given for illustration only and are not necessarily the maximum attainable;

(iv) the structures of the end-products of the Formula (I) were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(v) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis; and

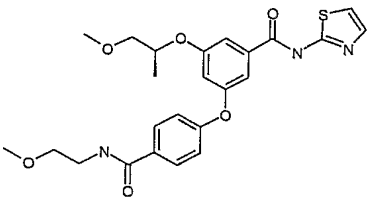
(vi) Biotage cartridges refer to pre-packed silica cartridges (from 40g up to 400g), eluted using a biotage pump and fraction collector system; Biotage UK Ltd, Hertford, Herts, UK.

Abbreviations

DCM	dichloromethane;
DEAD	diethylazodicarboxylate;
DIAD	diisopropylazodicarboxylate;
DMSO	dimethyl sulphoxide;
DMF	dimethylformamide;
EDAC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride;
HPLC	high pressure liquid chromatography
HPMC	Hydroxypropylmethylcellulose;
LCMS	liquid chromatography / mass spectroscopy;
NMR	nuclear magnetic resonance spectroscopy
RT	room temperature; and
THF	tetrahydrofuran

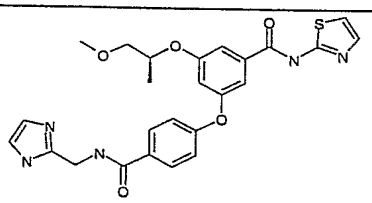
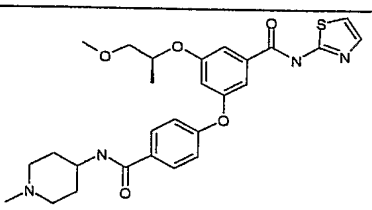
All compound names were derived using ACD NAME computer package.

Example 1: 3-(4-{[(2-Methoxyethyl)amino]carbonyl}phenoxy)-5-(2-(1S)-methoxy-(1-methylethyl)oxy)-N-1,3-thiazol-2-ylbenzamide



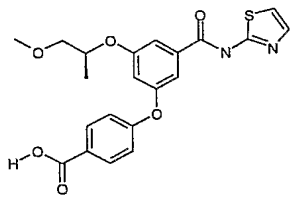
To a suspension of 4-({3-{[(1*S*)-2-methoxy-(1-methylethyl)oxy}-5-[(1,3-thiazol-2-ylamino) carbonyl] phenyl}oxy)benzoic acid (107 mg), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (122 mg) and 2-methoxyethylamine (38 mg) in DMF (2ml), was added diisopropylethylamine (0.11ml) and the mixture stirred at ambient temperature for 1 hour. Water (30ml) was added and the mixture extracted with ethyl acetate (3 x 15ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica with ethyl acetate as eluant to give the desired compound (63 mg). ^{1}H NMR δ (d_6-DMSO): 1.2 (d, 3H), 3.3 (s, 6H), 3.4-3.5 (m, 6H), 4.7-4.8 (m, 1H), 6.85 (s, 1H), 7.1 (d, 2H), 7.25 (m, 2H), 7.55 (d, 2H), 7.9 (d, 2H), 8.45 (s, 1H); *m/z* 486 $(M+H)^+$

In a similar manner to that described above, **Examples 1a & 1b** were also prepared:-

Example	Structure	*m/z*	NMR
1a		508 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.2 (d, 3H), 3.3 (s, 3H), 3.4-3.5 (d, 2H), 4.45 (d,2H), 4.7-4.8 (m, 1H), 6.85 (m, 3H), 7.1 (d, 2H), 7.25 (d, 2H), 7.55 (d, 2H) 7.95 (d, 2H), 8.95 (t, 1H)
1b		525 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.3 (d, 3H), 1.6-1.75 (m, 4H), 1.95-2.0 (m, 2H), 2.2 (s, 3H), 2.8 (d, 2H), 3.3 (s, 3H), 3.55 (m, 2H), 3.8 (m, 1H), 4.8 (m, 1H), 6.95 (s, 1H), 7.2 (d, 2H), 7.3 (m, 2H), 7.6 (d, 2H) 7.95 (d, 2H), 8.25 (d, 1H)

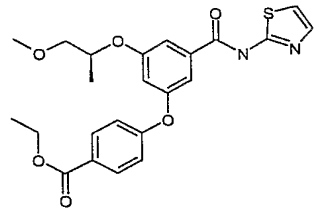
The required acid for Example 1 was prepared as described below:-

4-({3-{[(1*S*)-2-methoxy-(1-methylethyl)oxy}-5-[(1,3-thiazol-2-ylamino)carbonyl] phenyl}oxy)benzoic acid



A solution of ethyl 4-({3-{[(1*S*)-2-methoxy-(1-methylethyl)oxy}-5-[(1,3-thiazol-2-ylamino)carbonyl] phenyl}oxy)benzoate (334mg) in THF (10 ml) was added to a solution of lithium hydroxide monohydrate (82mg) in water (5ml). The mixture was stirred at ambient temperature for 16 hours and the THF removed *in vacuo*. The aqueous layer was acidified with 1M hydrochloric acid (1.83ml), and the solid precipitate filtered off, washed with water and dried *in vacuo* to give the desired compound (268mg). ^{1}H NMR δ (d_6-DMSO): 1.2 (d, 3H), 3.25 (s, 3H), 3.5 (m, 2H), 4.7-4.8 (m, 1H), 6.9 (t, 1H), 7.1 (d, 2H), 7.25 (d, 1H), 7.35 (s, 1H), 7.55 (d, 2H), 7.95 (d, 2H), 12.75 (s, 1H); *m/z* 429 $(M+H)^+$

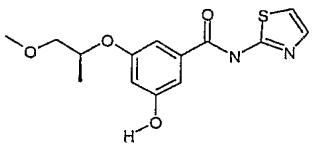
Ethyl 4-({3-{[(1*S*)-2-methoxy-(1-methylethyl)oxy}-5-[(1,3-thiazol-2-ylamino)carbonyl] phenyl}oxy)benzoate



A solution of 3-hydroxy-5-{[(1*S*)-2-methoxy-(1-methylethyl)oxy}-*N*-1,3-thiazol-2-ylbenzamide (1.0g), 4-ethoxycarbonylphenylboronic acid (1.18g), copper (II) acetate (1.19g), triethylamine (2.25ml) and freshly activated 4Å molecular sieves (4g) in dichloromethane (50ml) was stirred at ambient temperature and under ambient atmosphere for 2 days. The reaction mixture was filtered through diatomaceous earth, washed with dichloromethane (2 x 10ml), the dichloromethane removed *in vacuo* and the residual oil partitioned between ethyl acetate (75ml) and 1M hydrochloric acid (30ml). The ethyl acetate layer was separated, washed sequentially with aqueous sodium hydrogen carbonate solution and brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica with 30% ethyl acetate in isohexane as eluant to give the desired compound (700mg). ^{1}H NMR δ ($CDCl_3$): 1.3

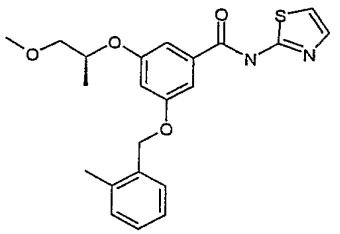
(d, 3H), 1.4 (t, 3H), 3.4 (s, 3H), 3.5-3.6 (m, 2H), 4.35 (q, 2H), 4.5-4.6 (m, 1H), 6.85 (s, 1H), 6.95 (d, 1H), 7.0 (d, 2H), 7.15 (s, 1H), 7.2 (d, 1H), 7.35 (d, 1H), 8.05 (d, 2H); *m/z* 457 $(M+H)^+$

3-Hydroxy-5-{[(1*S*)-2-methoxy-(1-methylethyl)oxy}-*N*-1,3-thiazol-2-ylbenzamide



A solution of 3-{[(1S)-2-methoxy-(1-methylethyl)oxy}-5-{[(2-methylphenyl)methyl]oxy}-*N*-1,3-thiazol-2-ylbenzamide (6.9g) and thioanisole (10ml) in trifluoroacetic acid (65ml) was stirred at ambient temperature for 16 hours. The trifluoroacetic acid was removed *in vacuo* and the residual oil partitioned between ethyl acetate (75ml) and aqueous sodium hydrogen carbonate solution (200ml). The aqueous layer was separated, extracted with ethyl acetate (2 x 75ml), and the combined organic extracts washed with brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica with 50% ethyl acetate in isohexane as eluant to give the desired compound (4.6g). ^1H NMR δ ($CDCl_3$): 1.3 (d, 3H), 3.4 (s, 3H), 3.5-3.6 (m, 2H), 4.5-4.6 (m, 1H), 6.65 (s, 1H), 6.95 (d, 1H), 7.05 (s, 1H), 7.1 (s, 1H), 7.25 (d, 1H); *m/z* 309 $(M+H)^+$

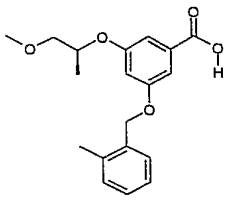
3-{[(1S)-2-Methoxy-(1-methylethyl)oxy}-5-{[(2-methylphenyl)methyl]oxy}-*N*-1,3-thiazol-2-ylbenzamide



To a solution of 3-[(1S)-2-methoxy-(1-methylethyl)oxy]-5-{[(2-methylphenyl)methyl]oxy} benzoic acid (9.55g) in dichloromethane (140ml) was added oxalyl chloride (2.83ml), followed by DMF (1 drop), and the mixture stirred at ambient temperature for 16 hours. The dichloromethane and excess oxalyl chloride were removed *in vacuo*, the residual oil dissolved in dichloromethane (25ml) and added to a solution of 2-aminothiazole (2.84g) and triethylamine (7.88ml) in dichloromethane (75ml) at 0-5°C, and the mixture stirred at ambient temperature for 4 hours. The dichloromethane and excess triethylamine were removed *in vacuo*, the residual oil partitioned between ethyl acetate (100ml) and 1M hydrochloric acid

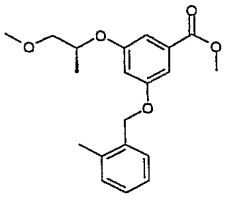
(100ml). The ethyl acetate layer was separated, washed sequentially with 1M hydrochloric acid, aqueous sodium hydrogen carbonate solution, and brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on alumina with ethyl acetate as eluant to give the desired compound (11.0g). ^1H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.35 (s,3H), 3.4 (s, 3H), 3.5-3.6 (m, 2H), 4.55-4.6 (m, 1H), 5.0 (s,2H), 6.8 (s, 1H), 6.95 (d, 1H), 7.15 (s, 1H), 7.25 (m, 5H), 7.4 (d, 1H); *m/z* 413 $(M+H)^+$

3-[(1S)-2-methoxy-(1-methylethyl)oxy]-5-{[(2-methylphenyl)methyl]oxy}benzoic acid



A solution of methyl 3-[{(1S)-2-methoxy-(1-methylethyl)oxy]-5-{[(2-methylphenyl) methyl] oxy}benzoate (10.65g) in THF (200 ml) and methanol (50ml) was added to a solution of lithium hydroxide monohydrate (6.0g) in water (100ml). The mixture was stirred at ambient temperature for 16 hours and the THF and methanol removed *in vacuo*. The aqueous layer was acidified to pH1 with hydrochloric acid, and extracted with ethyl acetate (3 x 50ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give the desired compound (9.55g); *m/z* 329 $(M-H)^-$

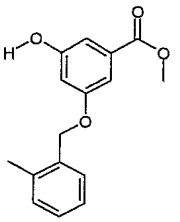
Methyl 3-[{(1S)-2-methoxy-(1-methylethyl)oxy]-5-{[(2-methylphenyl)methyl]oxy} benzoate



A stirred suspension of methyl 3-hydroxy-5-{[(2-methylphenyl)methyl]oxy}benzoate (15.27g) and polymer-supported triphenyl phosphine (39.2g) in dry dichloromethane (900 ml) was cooled in an ice-bath and diisopropyl azodicarboxylate (11.88ml) was added drop wise. The reaction mixture was stirred at 0-5°C for 30 minutes and (*R*)-1-methoxy-propan-2-ol was added dropwise. The reaction mixture was stirred at ambient temperature for 16 hours, filtered through diatomaceous earth and the dichloromethane evaporated to a residue which was chromatographed on silica with 10% ethyl acetate in isohexane as eluant to give the

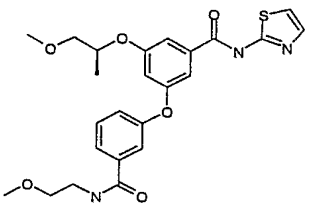
desired compound (10.65g). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.4 (s,3H), 3.4 (s, 3H), 3.5-3.6 (m, 2H), 3.9 (s, 3H), 4.55-4.6 (m, 1H), 5.0 (s,2H), 6.8 (s, 1H), 7.25 (m, 5H), 7.4 (d, 1H)

Methyl 3-hydroxy-5-{[(2-methylphenyl)methyl]oxy}benzoate



To a solution of methyl 3,5-dihydroxybenzoate (50g, 0.30M) in DMF (500ml) at 0°C was added sodium hydride (10.8 g, 0.27M) portionwise, maintaining the reaction temperature below 10°C. The reaction was allowed to warm to 15°C, and was stirred for 20 minutes. The mixture was cooled to 0°C and a solution of 2-methylbenzyl bromide (36ml, 0.27M) in DMF (50 ml) was added over 30 minutes. The reaction was warmed to ambient temperature and concentrated *in vacuo*, the residual oil partitioned between ethyl acetate (500ml) and water (250ml), the ethyl acetate layer separated, washed sequentially with water and brine, dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica eluting with a gradient of 0-100% ethyl acetate in isohexane to give the desired compound (21.9 g); ^{1}H NMR δ ($CDCl_3$) 2.39 (s, 3H), 3.90 (s, 3H), 5.02 (s, 2H), 5.61 (s, 1H), 6.69 (t, 1H), 7.15-7.42 (m, 6H)

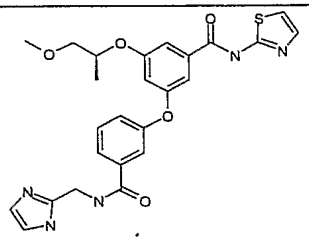
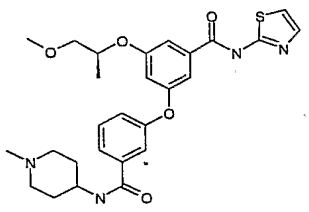
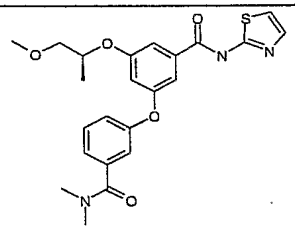
Example 2: 3-(3-{[(2-Methoxyethyl)amino]carbonyl}phenoxy)-5-[(1S)-2-methoxy-(1-methylethyl)oxy]-N-1,3-thiazol-2-ylbenzamide



To a suspension of 3-({3-{[(1S)-2-methoxy-(1-methylethyl)oxy}-5-[(1,3-thiazol-2-ylamino)carbonyl] phenyl}oxy)benzoic acid (107 mg), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (122 mg) and 2-methoxyethylamine (38 mg) in DMF (2ml) was added diisopropylethylamine (0.11ml) and the mixture stirred at ambient temperature for 1 hour. Water (30ml) was added and the mixture extracted with ethyl acetate

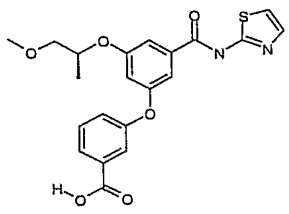
(3 x 15ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica, with ethyl acetate as eluant, to give the desired compound (85 mg). ^{1}H NMR δ (d_6-DMSO): 1.2 (d, 3H), 3.25 (s, 3H), 3.3 (s, 3H), 3.4-3.5 (m, 6H), 4.7-4.8 (m, 1H), 6.8 (s, 1H),7.2-7.25 (m, 3H), 7.55 (m, 4H), 7.7 (d, 1H) 8.55 (t, 1H), 12.6 (s, 1H); *m/z* 486 $(M+H)^+$

In a similar manner, **Examples 2a-2c** were also prepared:-

Example	Structure	*m/z*	NMR
2a		508 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.25 (d, 3H), 3.3 (s, 3H), 3.5 (m, 2H), 4.45 (d,2H), 4.7-4.8 (m, 1H), 6.8 (s, 1H), 6.85 (s, 2H), 7.2 (s, 1H), 7.25 (d, 2H), 7.5 (m, 3H), 7.6 (s, 1H),7.75 (d, 2H), 9.0 (t, 1H)
2b		525 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.25 (d, 3H), 1.5-1.6 (m, 2H), 1.7-1.8 (m, 2H), 1.9-2.0 (m, 2H), 2.15 (s, 3H), 2.75 (d, 2H), 3.3 (s, 3H), 3.5 (m, 2H), 3.6-3.8 (m, 1H), 4.8 (m, 1H), 6.8 (s, 1H), 7.2 (s, 1H), 7.25 (d, 2H), 7.35 (m, 4H), 7.7 (d, 1H), 8.25 (d, 1H)
2c		456 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.2 (d, 3H), 2.9-3.0 (d, 6H), 3.3 (s, 3H), 3.5 (m,2H), 4.7-4.8 (m, 1H), 6.8 (s, 1H), 7.05 (s, 1H), 7.2 (m, 2H), 7.25 (d, 2H), 7.5 (m, 3H), 12.6 (s, 1H)

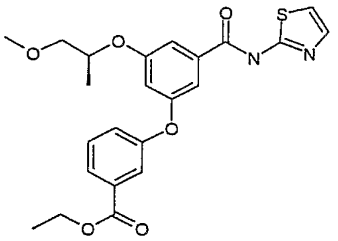
The required acid for Example 2 was prepared as described below:-

<u>3-({3-{[(1S)-2-methoxy-(1-methylethyl)oxy}-5-[(1,3-thiazol-2-ylamino)carbonyl] phenyl}oxy)benzoic acid</u>



A solution of ethyl 3-({3-{[(1S)-2-methoxy-(1-methylethyl)oxy}-5-[(1,3-thiazol-2-ylamino) carbonyl]phenyl}oxy)benzoate (319mg) in THF (10ml) was added to a solution of lithium hydroxide monohydrate (78mg) in water (5ml). The mixture was stirred at ambient temperature for 16 hours and the THF removed *in vacuo*. The aqueous layer was acidified with 1M hydrochloric acid (1.75ml), the solid precipitate filtered off, washed with water and dried *in vacuo* to give the desired compound (283mg). ^{1}H NMR δ (d_6-DMSO): 1.2 (d, 3H), 3.25 (s, 3H), 3.5 (m, 2H), 4.7-4.8 (m, 1H), 6.85 (t, 1H), 7.25 (m, 2H), 7.35 (dd, 1H), 7.55 (m, 4H), 7.75 (d, 1H); *m/z* 429 $(M+H)^+$

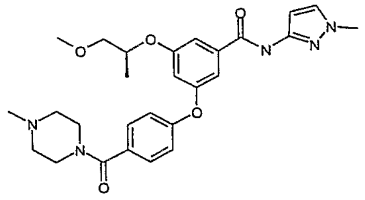
Ethyl 3-({3-{[(1S)-2-methoxy-(1-methylethyl)oxy}-5-[(1,3-thiazol-2-ylamino)carbonyl]phenyl}oxy)benzoate



A solution of 3-hydroxy-5-{[(1S)-2-methoxy-(1-methylethyl)oxy}-*N*-1,3-thiazol-2-ylbenzamide (1.0g), 3-ethoxycarbonylphenylboronic acid (1.18g), copper (II) acetate (1.19g), triethylamine (2.25ml) and freshly activated 4Å molecular sieves (4g) in dichloromethane (50ml) was stirred at ambient temperature and under ambient atmosphere for 2 days. The reaction mixture was filtered through diatomaceous earth, washed with dichloromethane (2 x 10ml), the dichloromethane removed *in vacuo,* and the residual oil partitioned between ethyl acetate (75ml) and 1M hydrochloric acid (30ml). The ethyl acetate layer was separated, washed sequentially with aqueous sodium hydrogen carbonate solution and brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica (eluting with 30% ethyl acetate in isohexane) to give the desired ester (680mg). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 1.4 (t, 3H), 3.4 (s, 3H), 3.5-3.6 (m, 2H), 4.35 (q, 2H), 4.5-4.6 (m, 1H), 6.8 (t, 1H), 6.95 (d, 1H), 7.1 (d, 1H), 7.2 (m, 2H), 7.3 (d, 1H), 7.4 (t, 1H), 7.7 (d, 1H), 7.85 (d, 1H), 11.6 (s, 1H); *m/z* 457 $(M+H)^+$

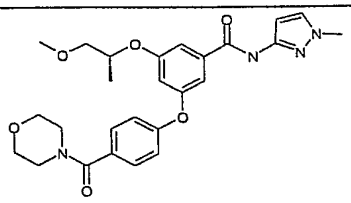
The synthesis of 3-hydroxy-5-{[(1S)-2-methoxy-(1-methylethyl)oxy}-*N*-1,3-thiazol-2-ylbenzamide is described above in Example 1.

Example 3: 3-[(1S)-2-Methoxy-(1-methylethyl)oxy]-5-{4-[(4-methylpiperazin-1-yl)carbonyl]phenoxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide



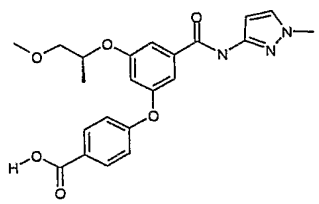
To a suspension of 4-[(3-{[(1S)-2-methoxy-(1-methylethyl)oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]benzoic acid (212 mg), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (400 mg) and *N*-Methylpiperazine (105 mg) in DMF (10ml), was added diisopropylethylamine (0.35ml) and the mixture stirred at ambient temperature for 24 hours. Water (30ml) was added and the mixture extracted with ethyl acetate (3 x 15ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica eluting with a gradient of 0-50% methanol in ethyl acetate to give the desired compound (130 mg). ^{1}H NMR δ ($CDCl_3$): 1.32 (d, 3H), 2.35 (s, 3H), 2.43 (m, 4H), 3.41 (s, 3H), 3.54 (m, 2H), 3.6-3.8 (m, 4H), 3.82 (s, 3H), 4.59 (m, 1H), 6.78 (m, 2H), 7.05 (t, 3H), 7.22 (m, 1H), 7.27 (m, 1H), 7.42 (d, 2H), 8.30 (br s, 1H); *m/z* 508 $(M+H)^+$

In a similar manner to that described above, **Example 3a** was also prepared:-

Example	Structure	*m/z*	NMR
3a 1		495 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.31 (d, 3H), 3.4 (s, 3H), 3.46-3.61 (m, 2H), 3.62-3.77 (m, 8H), 3.81 (s, 3H), 4.60 (m, 1H), 6.78 (m, 2H), 7.02 (s, 1H), 7.07 (m, 2H), 7.22 (m, 1H) 7.28 (m, 1H), 7.42 (d, 2H), 8.31 (br s, 1H)

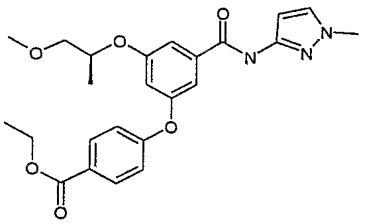
The required acid for Example 3 was prepared as described below:-

4-[(3-[(1S)-2-Methoxy-(1-methylethyl)oxy])-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]benzoic acid



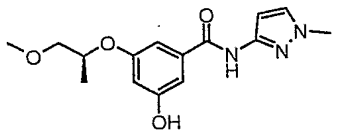
A solution of ethyl 4-[(3-[(1S)-2-methoxy-(1-methylethyl)oxy])-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]benzoate (5.45g) in THF (200 ml) was added to a solution of lithium hydroxide monohydrate (2.52g) in water (100ml). The mixture was stirred at ambient temperature for 48 hours and the THF removed *in vacuo*. The aqueous layer was acidified with 1M hydrochloric acid (60ml), and the solid precipitate filtered off, washed with water and dried *in vacuo* to give the desired acid (5g). ^{1}H NMR δ (d_6-DMSO): 1.22 (d, 3H), 3.26 (s, 3H), 3.45 (m, 2H), 3.75 (s, 3H), 4.71 (m, 1H), 6.51 (m, 1H), 6.84 (m, 1H), 7.08 (d, 2H), 7.24 (m, 1H), 7.44 (s, 1H), 7.57 (m, 1H), 7.95 (d, 2H), 10.84 (br s, 1H), 12.80 (br s, 1H); *m/z* 426 $(M+H)^+$

Ethyl 4-[(3-[(1S)-2-methoxy-(1-methylethyl)oxy])-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]benzoate



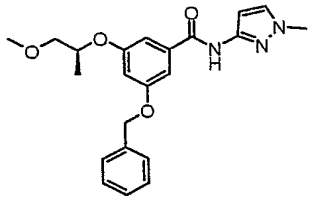
A solution of 3-hydroxy-5-[(1S)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (10.0g), 4-ethoxycarbonylphenylboronic acid (9.4g), copper (II) acetate (9g), triethylamine (23ml) and freshly activated 4Å molecular sieves (36g) in dichloromethane (500ml) was stirred at ambient temperature and under ambient atmosphere for 2 days. The reaction mixture was filtered through celite, washed with dichloromethane (2 x 50ml), the dichloromethane removed *in vacuo* and the residual oil partitioned between ethyl acetate (500ml) and 1M hydrochloric acid (200ml). The ethyl acetate layer was separated, washed sequentially with aqueous sodium hydrogen carbonate solution and brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica eluting with a gradient of 50-100% ethyl acetate in isohexane to give the desired compound (5.47g). ^{1}H NMR δ ($CDCl_3$): 1.3 (m, 3H), 1.41 (t, 3H), 3.39 (s, 3H), 3.49 (m, 1H), 3.58 (m, 1H), 3.78 (s, 3H), 4.38 (q, 2H), 4.58 (m, 1H), 6.79 (m, 2H), 7.01-7.1 (m, 3H), 7.26 (m, 2H), 8.01 (m, 2H), 8.61 (br s, 1H); *m/z* 454 $(M+H)^+$

3-Hydroxy-5-[(1S)-2-methoxy-(1-methylethyl)oxyl-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



To a solution of 3-[(1S)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (7.07g) in THF (50ml) and methanol (50ml) was added 10% palladium on carbon (727mg) as a slurry in THF (1 ml) and methanol (1 ml). The mixture was placed under vacuum and stirred under an atmosphere of hydrogen for 70 hours. The mixture was filtered through diatomaceous earth, and the diatomaceous earth washed with methanol (2 x 100 ml), followed by evaporation *in vacuo*. The residues were dissolved in ethyl acetate (10 ml), treated with isohexane (40 ml), the solid filtered off and washed with isohexane (50 ml) to afford the desired compound (5.17g) which was used without further purification. ^{1}H NMR δ (d_6-DMSO): 1.22 (d, 3H), 3.28 (s, 3H, obscured by water), 3.38-3.53 (m, 2H), 3.76 (s, 3H), 4.65 (m, 1H), 6.44 (m, 1H), 6.54 (m, 1H), 6.93 (s, 1H), 7.04 (s, 1H), 7.57 (m, 1H), 9.63 (br s, 1H), 10.60 (s, 1H); *m/z* 306 $(M+H)^+$, 304 $(M-H)^-$

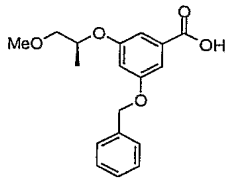
3-[(1S)-2-methoxy-(1-methylethyl)oxyl-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide



A solution of 3-[(1S)-2-methoxy-(1-methylethyl)oxy]-5-{[phenylmethyl]oxy}benzoic acid (8.73g) in dichloromethane (150 ml) was cooled to 0°C. Oxalyl chloride (4.81 ml) and DMF (0.15ml) were slowly added with stirring. The mixture was allowed to warm to ambient temperature and stirred for 16 hours, following which the organics were removed *in vacuo*, and the residues azeotroped with toluene (75ml). The crude material was dissolved in dichloromethane (75 ml) and slowly added to a stirred suspension of 1-methyl-1*H*-pyrazol-3-amine (3.35g) and diisopropylethylamine (14.4 ml) in dichloromethane (75 ml). The mixture was stirred at ambient temperature for 18 hours, before the organics were evaporated *in vacuo* and the residue dissolved in ethyl acetate (150 ml). The organics were washed with 1M aqueous hydrochloric acid (100 ml) and brine (50 ml), and dried ($MgSO_4$), before evaporation

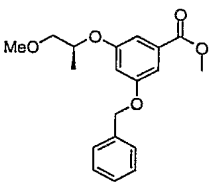
in vacuo to give crude material. This was chromatographed on a 200g Biotage Flash 75 SiO_2 column (eluting with 30 to 90% ethyl acetate in isohexane), and evaporated *in vacuo* to afford the desired compound (7.07g). ^{1}H NMR δ (d_6-DMSO): 1.23 (d, 3H), 3.28 (s, 3H, obscured by water), 3.40-3.52 (m, 2H), 3.77 (s, 3H), 4.70 (m, 1H), 5.03 (s, 2H), 6.56 (m, 1H), 6.71 (m, 1H), 7.18 (s, 1H), 7.24 (s, 1H), 7.32-7.47 (br m, 5H), 7.58 (m, 1H), 10.73 (s, 1H); *m/z* 396 $(M+H)^+$.

3-[(1S)-2-methoxy-(1-methylethyl)oxy]-5-{[phenylmethyl]oxy}benzoic acid



A solution of methyl 3-[(1S)-2-methoxy-(1-methylethyl)oxy]-5-{[phenylmethyl]oxy} benzoate (77.4 mmol) in a mixture of THF (232 ml) and methanol (232 ml) was treated with a solution of 2M sodium hydroxide (232 mmol), and the reaction mixture stirred for 4 hours at ambient temperature. The resulting solution was diluted with water (250 ml) and most of the organic solvent removed *in vacuo*. The resulting suspension was washed with diethyl ether (3 x 200 ml) and the organic washings discarded. The resulting aqueous solution was acidified to pH4 with 2M hydrochloric acid solution and extracted with ethyl acetate (2 x 200 ml). The extracts were combined, washed with brine, dried ($MgSO_4$), and evaporated to give the desired compound (99% yield). ^{1}H NMR δ (d_6-DMSO): 1.20 (d, 3H), 3.46 (m, 2H), 4.64 (m, 1H), 5.15 (s, 2H), 6.83 (app t, 1H), 7.06 (s, 1H), 7.13 (s, 1H), 7.30-7.49 (m, 5H), 12.67 (br s, 1H)

Methyl 3-[(1S)-2-methoxy-(1-methylethyl)oxyl-5-{[phenylmethyl]oxy}benzoate

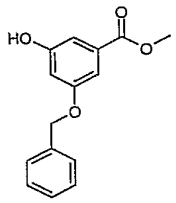


To a solution of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate (77.4 mmol) in THF was added polymer-supported triphenylphosphine (51.7g of 3 mmol/g loading, 155mmol) and (*R*)-(-)-1-methoxy-2-propanol (102 mmol). The stirred solution was blanketed with argon and cooled in an ice bath. A solution of diisopropylazodicarboxylate (116 mmol) was added

dropwise by syringe over 10 minutes. The solution was stirred for 20 minutes and filtered, washing the residue with THF (500 ml). The filtrate and washings were combined, and evaporated to give the desired compound which was used without further purification. ^{1}H NMR δ (d_6-DMSO): 3.26 (s, 3H), 3.44 (m, 2H), 3.82 (s, 3H), 4.63 (m, 1H), 5.14 (s, 2H), 6.85 (s, 1H), 7.05 (s, 1H), 7.11 (s, 1H), 7.30-7.47 (m, 5H)

The ^{1}H NMR spectrum also contained signals consistent with a small amount of bis(1-methylethyl)hydrazine-1,2-dicarboxylate.

Methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate



To a stirred solution of methyl 3,5-dihydroxybenzoate (5.95 mol) in DMF (6 L) was added potassium carbonate (9 mol), and the suspension stirred at ambient temperature under argon. To this was added benzyl bromide (8.42 mol) slowly over 1 hour, with a slight exotherm, and the reaction mixture stirred overnight at ambient temperature. The reaction was quenched cautiously with ammonium chloride solution (5 L) followed by water (35 L). The aqueous suspension was extracted with dichloromethane (1 x 3 L and 2 x 5 L). The combined extracts were washed with water (10 L) and dried overnight ($MgSO_4$). The solution was evaporated in *vacuo*, and the crude product chromatographed in 3 batches (flash column, 3 x 2 kg silica, eluting with a gradient consisting of hexane containing 10% dichloromethane, to neat dichloromethane, to dichloromethane containing 50% ethyl acetate) to eliminate starting material. The crude eluant was further chromatographed in 175 g batches (Amicon HPLC, 5 kg normal-phase silica, eluting with isohexane containing 20% v/v of ethyl acetate) to give the desired compound (21% yield). ^{1}H NMR δ (d_6-DMSO): 3.8 (s, 3H), 5.1 (s, 2H), 6.65 (m, 1H), 7.0 (m, 1H), 7.05 (m, 1H), 7.3-7.5 (m, 5H), 9.85 (br s, 1H)

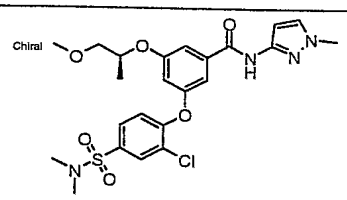
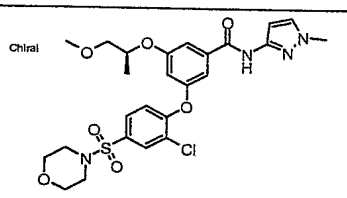
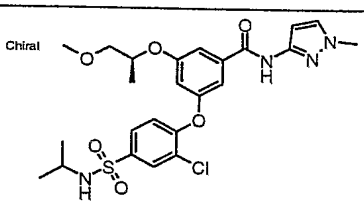
Example 4: General Procedure for Preparation of Halogenated Sulphonamides

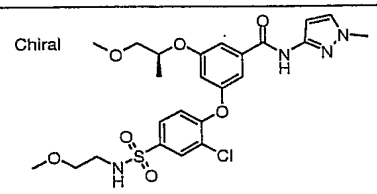
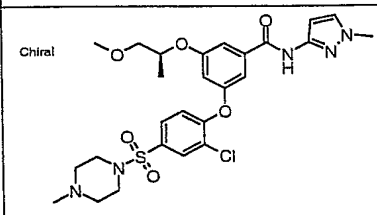
To a solution of the appropriate amine (1.8 mmol) in dichloromethane (2 ml), was added the sulphonyl chloride (0.72 mmol) in dichloromethane (2 ml), and the resulting mixture stirred for 18 hours. The mixture was treated with 1M aqueous hydrochloric acid (4 ml) and the

organics separated. Evaporation *in vacuo* gave the crude fluorosulphonamide which was used without further purification.

To a solution of the crude fluorosulphonamide (7.2 mmol) in acetonitrile (3 ml), was added 3-hydroxy-5-[(1S)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (0.36 mmol) and potassium carbonate (1.8 mmol). The mixture was heated to 170°C in a 'Smith Creator Microwave' for 100 minutes, before being filtered and the resultant organics evaporated *in vacuo*. The residues were then chromatographed on a Redisep (12g, SiO_2) cartridge using an Isco Optix chromatography system, eluting with 30 to 100% ethyl acetate in isohexane, and evaporated *in vacuo* to afford the desired compound.

Examples 4a-4e were synthesised using the generic preparation described above:-

Example	Structure	*m/z*	NMR
4a		523, 525 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.24 (d, 3H), 2.65 (s, 6H), 3.27 (s, 3H, obscured by water), 3.42-3.54 (m, 2H), 3.76 (s, 3H), 4.72-4.81 (m, 1H), 6.55 (m, 1H), 6.93 (m, 1H), 7.20 (d, 1H), 7.26 (s, 1H), 7.48 (s, 1H), 7.58 (m, 1H), 7.70 (dd, 1H), 7.91 (m, 1H), 10.84 (s, 1H)
4b		565, 567 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.24(d, 3H), 2.93 (t, 4H), 3.26 (s, 3H, obscured by water), 3.43-3.54 (m, 2H), 3.63 (t, 4H), 3.77 (s, 3H), 4.78 (m, 1H), 6.54 (m, 1H), 6.95 (m, 1H), 7.22 (d, 1H), 7.28 (s, 1H), 7.50 (m, 1H), 7.58 (m, 1H), 7.68 (dd, 1H), 7.90 (d, 1H), 10.84 (s, 1H)
4c		537, 539 $(M+H)^+$ 535, 537 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 0.95 (d, 6H), 1.23 (d, 3H), 3.27 (s, 3H, obscured by water), 3.27 (m, 1H, obscured by water), 3.42-3.53 (m, 2H), 3.76 (s, 3H), 4.75 (m, 1H), 6.54 (m, 1H), 6.89 (m, 1H), 7.21 (s, 2H), 7.46 (s, 1H), 7.57 (m, 1H), 7.67 (d, 1H), 7.76 (dd, 1H), 7.95 (d, 1H), 10.84 (s, 1H)

4d	Chiral 	553, 555 $(M+H)^+$ 551, 553 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 1.23 (d, 3H), 2.96 (m, 2H), 3.09 (m, 2H), 3.14 (s, 3H), 3.28 (s, 3H, obscured by water), 3.48 (m, 2H), 3.76 (s, 3H), 4.75 (m, 1H), 6.53 (m, 1H), 7.89 (m, 1H), 7.17-7.24 (m, 2H), 7.46 (m, 1H), 7.57 (m, 1H), 7.73 (dd, 1H), 7.82 (m, 1H), 7.96 (m, 1H), 10.84 (s, 1H)
4e[$]	Chiral 	578, 580 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.24 (d, 3H), 2.13 (s, 3H), 2.35 (t, 4H), 2.94 (m, 4H), 3.28 (s, 3H, obscured by water), 3.42-3.53 (m, 2H), 3.75 (s, 3H), 4.76 (m, 1H), 6.54 (m, 1H), 6.93 (m, 1H), 7.21 (d, 1H), 7.28 (s, 1H), 7.49 (s, 1H), 7.58 (m, 1H), 7.69 (dd, 1H), 7.90 (m, 1H), 10.84 (s, 1H)

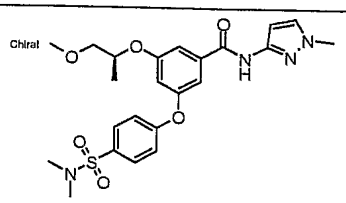
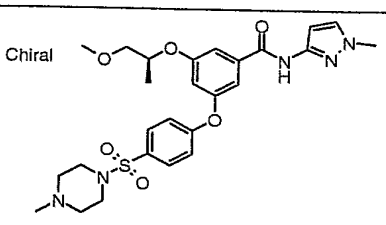
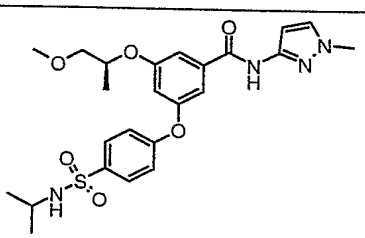
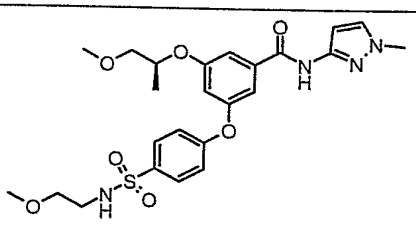
[$]The requisite sulphonamide for this example was prepared using a 1:1 ratio of amine : sulphonyl chloride, and isolated by treatment with 1M aqueous sodium hydroxide

The synthesis of 3-hydroxy-5-[(1S)-2-methoxy-(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide is described in Example 3 above.

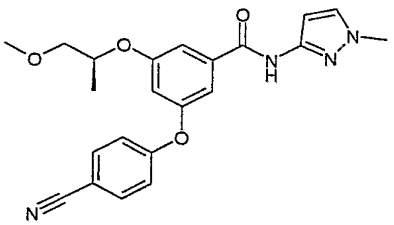
Example 5: General Procedure for Preparation of Sulphonamides

A solution of the requisite chlorosulphonamide from Example 4 above (0.12 mmol) in THF (5 ml) and methanol (5 ml) was treated with 10% palladium on carbon (6 mg) and triethylamine (0.1 ml). The flask was put under vacuum, and stirred under an atmosphere of hydrogen gas. The resulting mixture was stirred at ambient temperature until starting material was consumed, before being filtered through diatomaceous earth and washed with methanol. Evaporation of the organics in vacuo, and azeotroping with diethyl ether (3 x 5ml), followed by drying in vacuo, afforded the desired compound.

Examples 5a-5d were synthesised using the generic procedure described above:-

Example	Structure	*m/z*	NMR
5a		489 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.23 (d, 3H), 2.60 (s, 6H), 3.27 (s, 3H, obscured by water), 3.43-3.54 (m, 2H), 3.75 (s, 3H), 4.75 (m, 1H), 6.54 (m, 1H), 6.91 (m, 1H), 7.21 (d, 2H), 7.29 (s, 1H), 7.48 (s, 1H), 7.58 (m, 1H), 7.75 (d, 2H), 10.84 (s, 1H)
5b		544 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.24 (d, 3H), 2.13 (s, 3H), 2.36 (s, 4H), 2.88 (s, 4H), 3.28 (s, 3H, obscured by water), 3.43-3.54 (m, 2H), 3.76 (s, 3H), 4.75 (m, 1H), 6.55 (m, 1H), 6.92(s, 1H), 7.22 (d, 2H), 7.30 (s, 1H), 7.49 (s, 1H), 7.58 (m, 1H), 7.75 (d, 2H), 10.84 (s, 1H)
5c		503 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 0.96 (d, 6H), 1.23 (d, 3H), 3.20 (m, 1H), 3.28 (s, 3H, obscured by water), 3.42-3.53 (m, 2H), 3.76 (s, 3H), 4.55 (m, 1H), 6.55 (m, 1H), 7.88 (m, 1H), 7.18 (d, 2H), 7.25 (s, 1H), 7.46 (s, 1H), 7.50 (d, 1H), 7.59 (m, 1H), 7.81 (d, 2H), 10.84 (s, 1H)
5d		519 $(M+H)^+$ 517 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 1.24 (d, 3H), 2.91 (m, 2H), 3.10 (m, 2H), 3.16 (s, 3H), 3.28 (s, 3H, obscured by water), 3.43-3.52 (m, 2H), 3.76 (s, 3H), 4.76 (m, 1H), 6.53 (, m, 1H), 6.87 (m, 1H), 7.19 (d, 2H), 7.25 (s, 1H), 7.45 (s, 1H), 7.57 (m, 1H), 7.64 (m, 1H), 7.80 (d, 2H), 10.84 (s, 1H)

Example 6: 3-(4-Cyanophenoxy)-5-[(1S)-2-methoxy-(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide

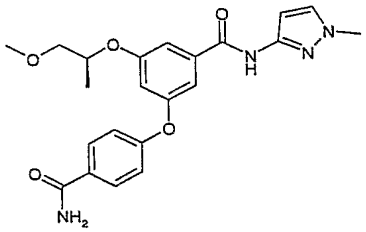


To a stirred solution of 3-hydroxy-5-[(1S)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (0.164 mmol) in DMF (1 ml) was added a 1M solution of sodium hexamethyldisilazide in THF (0.164 mmol). The reaction was stirred at room temperature for 10 minutes before adding 4-fluorobenzonitrile (0.164 mmol) The reaction was stirred

overnight at room temperature, then heated to 60°C and stirred for a further 4 hours. The reaction was allowed to cool to room temperature, and treated with a further 0.2 equivalents of 4-fluorobenzonitrile and sodium hexamethyldisilazide, heated to 70°C and stirred at this temperature for 3 hours. The reaction was cooled to room temperature, and treated with a further 0.2 equivalents of sodium hexamethyldisilazide, warmed to 70°C, and stirred at this temperature overnight . The solvent was removed *in vacuo* and the residual oil partitioned between ethyl acetate and water. The water layer was separated and re-extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated to a residue which was chromatographed on silica, using 0-1% methanol in dichloromethane as the eluent, to give the desired product (60% yield). ^1H NMR δ ($CDCl_3$): 1.35 (d, 3H), 3.40 (s, 3H), 3.55 (m, 2H), 3.78 (s, 3H), 4.60 (m, 1H), 6.80 (m, 2H), 7.10 (m, 3H), 7.30 (m, 2H), 7.62 (d, 2H), 8.55 (br s, 1H); *m/z* 407 $(M+H)^+$, 405 $(M-H)^-$

The synthesis of 3-hydroxy-5-[(1S)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide is described in Example 3 above.

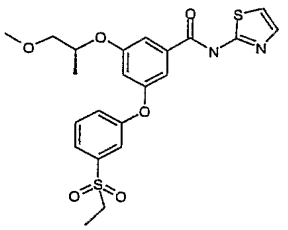
Example 7: 3-{[4-(Aminocarbonyl)phenyl]oxy}-5-[(1S)-2-methoxy-(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide



A suspension of 3-(4-cyanophenoxy)-5-[(1S)-2-methoxy-(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide (0.25 mmol), prepared as described in Example 6 above, sodium azide (0.28 mmol) and zinc bromide (0.25 mmol) in water (2ml) was heated to reflux and stirred at this temperature overnight. Isopropanol (2 ml) was added, and the reaction heated at reflux for a further 24 hours. The reaction was cooled to room temperature, evaporated to half volume *in vacuo,* and the residue partitioned between ethyl acetate and water. The water layer was separated and re-extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated to a residue which was chromatographed on silica with 0-10% methanol in dichloromethane as eluent to yield crude material. This material was dissolved in ethyl acetate and washed twice with 2M sodium hydroxide. The

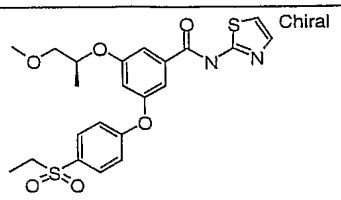
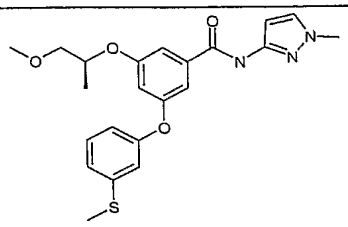
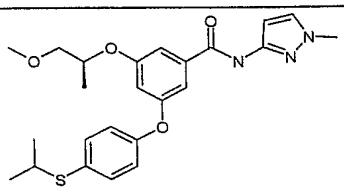
organic layer was washed with brine, dried ($MgSO_4$), filtered and evaporated. This material was dissolved in dichloromethane and purified using an 'Isolute-NH2' ion-exchange column eluting with 10% methanol:dichloromethane to yield the desired product. ^1H NMR δ ($CDCl_3$): 1.30 (d, 3H), 3.40 (s, 3H), 3.50 (m, 2H), 3.75 (s, 3H), 4.60 (m, 1H), 6.80 (m, 2H), 7.00 (d, 2H), 7.05 (s, 1H), 7.25 (m, 2H), 7.80 (d, 2H), 8.75 (br s, 1H); *m/z* 423 $(M-H)^-$

Example 8: 3-[3-(Ethylsulfonyl)phenoxy]- 5-[(1S)-2-methoxy-(1-methylethyl)oxy]-N-1,3-thiazol-2-ylbenzamide



A solution of 3-hydroxy-5-[(1S)-2-methoxy-(1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide (154 mg), 3-ethanesulphonylbenzeneboronic acid (203 mg), copper (II) acetate (183 mg), triethylamine (0.345ml) and freshly activated 4Å molecular sieves (1g) in dichloromethane (10ml), was stirred at ambient temperature and under ambient atmosphere for 3 days. The reaction mixture was filtered through diatomaceous earth, washed with dichloromethane (2 x 10ml), the dichloromethane removed *in vacuo* and the residual oil partitioned between ethyl acetate (50ml) and 1M hydrochloric acid (35ml). The ethyl acetate layer was separated, washed sequentially with saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$) and evaporated to a residue which was chromatographed on alumina with 5% methanol in ethyl acetate as eluant. Further chromatography on silica with 50% ethyl acetate in isohexane as eluant gave the desired compound (108 mg). ^1H NMR δ ($CDCl_3$): 1.2-1.35 (m, 6H), 3.15 (q, 2H), 3.4 (s, 3H), 3.5-3.6 (m, 2H), 4.5-4.6 (m, 1H), 6.8 (s, 1H), 7.0 (d, 1H), 7.2 (d, 1H), 7.25 (d, 1H), 7.3 (d, 1H), 7.35 (d, 1H), 7.55 (d, 2H), 8.05 (d, 1H); *m/z* 477 $(M+H)^+$

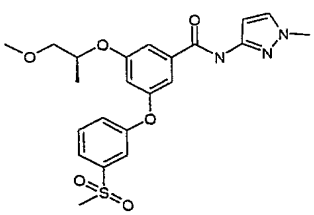
The following compounds were also prepared in an analogous fashion from 3-hydroxy-5-[(1S)-2-methoxy-(1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide, or from 3-hydroxy-5-[(1S)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide:

Example	Structure	*m/z*	NMR
8a	 Chiral	477 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.2-1.35 (m, 6H), 3.15 (q, 2H), 3.4 (s, 3H), 3.5-3.6 (m, 2H), 4.5-4.6 (m, 1H), 6.8 (s, 1H), 6.95 (d, 1H), 7.2 (d, 2H), 7.25 (d, 2H), 7.4 (s, 1H), 7.85 (d, 2H)
8b		428 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.22 (d, 3H), 2.45 (s, 3H), 3.30 (s, 3H), 3.46 (m, 2H), 3.76 (s, 3H), 4.72 (m, 1H), 6.53 (m, 1H), 6.72 (m, 1H), 6.80 (m, 1H), 6.94 (m, 1H), 7.05 (d, 1H), 7.12 (s, 1H), 7.34 (t, 1H), 7.39 (s, 1H), 7.57 (m, 1H), 10.81 (bs, 1H)
8c		456 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.11 (m, 9H), 3.26 (s, 3H), 3.37 (m, 1H), 3.45 (m, 2H), 3.76 (s, 3H), 4.72 (m, 1H), 6.53 (m, 1H), 6.74 (m, 1H), 7.02 (d, 2H), 7.16 (s, 1H), 7.39 (m, 1H), 7.42 (d, 2H), 7.57 (m, 1H), 10.81 (bs, 1H)

The syntheses of 3-hydroxy-5-[(1S)-2-methoxy-(1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide and 3-hydroxy-5-[(1S)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide are described in Examples 1 and 3 respectively.

Example 9a: 3-[(1S)-2-Methoxy-(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)-5-[3-(methylsulfonyl)phenoxy]benzamide

Example 9b: 3-[(1S)-2-Methoxy-(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)-5-[3-(methylsulfinyl)phenoxy]benzamide

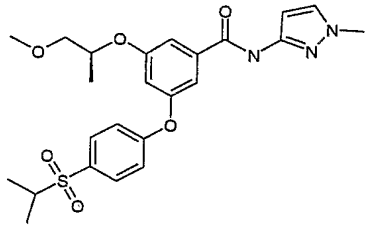
 &

To a solution of 3-[(1S)-2-methoxy-(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)-5-{[3-(methylthio)phenyl]oxy}benzamide (prepared as described in Example 8b above, 270mg) in dichloromethane (5 ml) was added *m*-chloroperbenzoic acid (1.3 equivalents) and the reaction stirred at room temperature for 1 hour. A further 1.4 equivalents of *m*-chloroperbenzoic acid

was added, and the reaction stirred at room temperature for a further 30 minutes. The reaction was added to saturated aqueous sodium metabisulphite and stirred for 20 minutes. The organic layer was separated, washed with brine, dried (MgSO4), and evaporated to a white foam. The crude mixture was purified using a 20g Redisep column eluting with 0-5% methanol in dichloromethane to yield the desired sulphone (117mg). ^{1}H NMR δ (d_6-DMSO): 1.12 (d, 3H), 3.22 (s, 3H), 3.26 (s, 3H), 3.47 (m, 2H), 3.75 (s, 3H), 4.75 (m, 1H), 6.54 (m, 1H), 6.85 (m, 1H), 7.23 (s, 1H), 7.40 (m, 1H), 7.45 (s, 1H), 7.52 (m, 1H), 7.57 (m, 1H), 7.68 (m, 2H), 10.84 (br s, 1H); *m/z* 460 $(M+H)^+$

A further fraction yielded the desired sulphoxide (105mg). ^{1}H NMR δ (d_6-DMSO): 1.12 (d, 3H), 2.75 (s, 3H), 3.26 (s, 3H), 3.47 (m, 2H), 3.76 (s, 3H), 4.73 (m, 1H), 6.53 (m, 1H), 6.80 (m, 1H), 7.19 (m, 2H), 7.33 (m, 1H), 7.44 (m, 2H), 7.59 (m, 2H), 10.83 (br s, 1H); *m/z* 444 $(M+H)^+$

Example 10: 3-({4-[(1-methylethyl)sulfonyl] phenyl}oxy)-5-[(1S)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



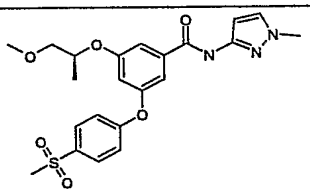
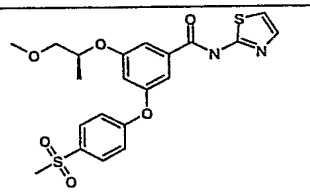
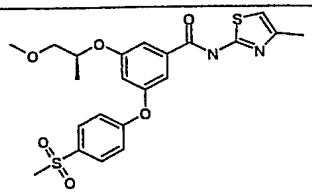
In a similar manner to that described above for Example 9, 3-({4-[(1-methylethyl)sulfonyl] phenyl}oxy)-5-[(1S)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide was prepared from 3-({4-[(1-methylethyl)thio]phenyl}oxy)-5-[(1S)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide. ^{1}H NMR δ (d_6-DMSO): 1.32 (m, 9H), 3.27 (m, 1H), 3.41 (s, 3H), 3.50 (dd, 1H), 3.58 (dd, 1H), 3.80 (s, 3H), 4.61 (m, 1H), 6.82 (m, 2H), 7.09 (d, 2H), 7.17 (m, 1H), 7.28 (m, 1H), 7.33 (m, 1H), 7.84 (d, 2H), 8.86 (br s, 1H); *m/z* 488 $(M+H)^+$

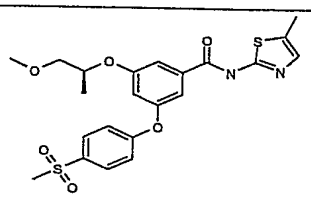
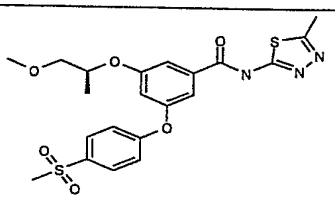
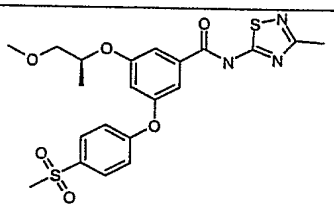
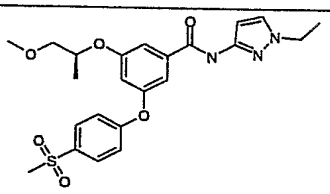
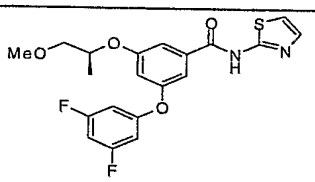
The synthesis of 3-({4-[(1-methylethyl)thio]phenyl}oxy)-5-[(1S)-2-methoxy-(1-methylethyl) oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide is described in Example 8c above.

Example 11: General Procedure for Amide Synthesis – HATU Coupling

Diisopropylethylamine (2.5 equivalents) was added to a suspension of 3-{(1S)-2-methoxy-(1-methylethyl)oxy}-5-{[4-(methylsulfonyl)phenyl] oxy}benzoic acid (1 equivalent), *O*-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexofluorophosphate (1.25 equivalents) and amine (1.25 equivalents) in DMF (20ml). The initial suspension dissolved into a dark orange solution. The resulting mixture was stirred at ambient temperature for 2 hours. The DMF was removed *in vacuo,* and the residue azeotroped with toluene. Water was added and the mixture extracted with ethyl acetate. The extracts were combined and washed sequentially with 1M hydrochloric acid, saturated sodium hydrogen carbonate solution and brine. The solution was dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give the crude product which was chromatographed (50% ethyl acetate in isohexane) to give desired compound (40-70% yield).

Examples 11a-11h were prepared using an analogous method to that described above from the appropriate acid and amino heterocycle:

Example	Structure	*m/z*	NMR
11a		460 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.2 (d, 3H), 3.2 (s, 3H), 3.25 (s, 3H), 3.5 (m, 2H), 3.8 (s, 3H), 4.75 (m, 1H), 6.55 (s, 1H), 6.9 (s, 1H), 7.2 (d, 2H), 7.3 (s, 1H), 7.45 (s, 1H), 7.6 (s, 1H), 7.9 (d, 2H), 10.85 (br s, 1H)
11b		463 $(M+H)^+$ 461 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 1.2 (d, 3H), 3.2 (s, 3H), 3.25 (s, 3H), 3.5 (m, 2H), 4.75 (m, 1H), 6.9 (s, 1H), 7.2 (d, 2H), 7.3 (s, 1H), 7.4 (s, 1H), 7.55 (d, 1H), 7.6 (s, 1H), 7.9 (d, 2H), 12.6 (br s, 1H)
11c		477 $(M+H)^+$ 475 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 1.2 (d, 3H), 2.25 (s, 3H), 3.2 (s, 3H), 3.25 (s, 3H), 3.5 (m, 2H), 4.75 (m, 1H), 6.8 (s, 1H), 6.95 (s, 1H), 7.2 (d, 2H), 7.3 (s, 1H), 7.4 (s, 1H), 7.95 (d, 2H), 12.6 (br s, 1H)

11d		477 $(M+H)^+$ 475 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 1.2 (d, 3H), 2.4 (s, 3H), 3.2 (s, 3H), 3.25 (s, 3H), 3.5 (m, 2H), 4.75 (m, 1H), 6.95 (s, 1H), 7.2 (s, 1H), 7.25 (d, 2H), 7.4 (s, 1H), 7.6 (s, 1H), 7.95 (d, 2H), 12.4 (br s, 1H)
11e		478 $(M+H)^+$ 476 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 1.2 (d, 3H), 2.6 (s, 3H), 3.2 (s, 3H), 3.25 (s, 3H), 3.5 (m, 2H), 4.75 (m, 1H), 7.0 (s, 1H), 7.2 (d, 2H), 7.4 (s, 1H), 7.6 (s, 1H), 7.95 (d, 2H)
11f		478 $(M+H)^+$ 476 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 1.2 (d, 3H), 2.5 (s, 3H), 3.2 (s, 3H), 3.25 (s, 3H), 3.5 (m, 2H), 4.75 (m, 1H), 7.0 (s, 1H), 7.2 (d, 2H), 7.4 (s, 1H), 7.6 (s, 1H), 7.95 (d, 2H), 13.5 (br s, 1H)
11g[$]		474 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.24 (d, 3H), 1.38 (t, 3H), 3.20 (s, 3H), 3.30 (s, 3H), 3.51 (m, 2H), 4.06 (s, 3H), 4.79 (m, 1H), 6.58 (s, 1H), 6.92 (s, 1H), 7.26 (d, 2H), 7.30 (s, 1H), 7.50 (s, 1H), 7.56 (s, 1H), 7.96 (d, 2H), 10.89 (s, 1H)
11h		421 $(M+H)^+$ 419 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 1.24 (d, 3H), 3.29 (s, 3H obscured by solvent peak), 3.48 (m, 2H), 4.76 (m, 1H), 6.83 (dd, 2H), 6.94 (m, 1H), 7.04 (m, 1H), 7.27 (m, 1H), 7.33 (m, 1H), 7.54 (d, 2H), 12.62 (bs, 1H)

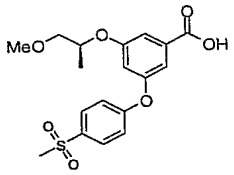
[$]The required amino pyrazole was prepared as follows. Sodium hydride (60% dispersion in mineral oil, 39 mg, 0.973 mmol), was added to 5-nitro-1*H*-pyrazole (100 mg, 0.885 mmol) in dry DMF (2 ml) under an argon atmosphere. The solution was stirred for 5 minutes, then ethyl iodide (0.85 ml, 1.062 mmol) added and the reaction warmed to 80°C for 3 hours. Saturated aqueous sodium hydrogen carbonate (30ml) was added, and the mixture extracted with diethyl ether (40 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to a residue which was purified by chromatography on silica (eluting with isohexane containing ethyl acetate, 33% v/v) to give the alkylated pyrazole (80 mg) which was

used in the next step without further purification. ^{1}H NMR δ ($CDCl_3$): 1.58 (t, 3H), 4.26 (q, 2H), 6.91 (d, 1H), 7.48 (d, 1H).

To a solution of the alkylated pyrazole (70 mg, 0.50 mmol) in THF (5 ml) under an inert atmosphere was added 10% palladium on carbon (15 mg). The flask was evacuated and refilled 3 times with hydrogen gas, and stirred vigourously at room temperature for 3 hours. The reaction mixture was refilled with argon, and a further portion of 10% palladium on carbon (50 mg) added, followed by refilling as above with a hydrogen atmosphere. The reaction was stirred for 16 hours, filtered through diatomaceous earth, and evaporated to afford the title compound (56 mg) as a colourless oil which was used without further purification. ^{1}H NMR δ ($CDCl_3$): 1.42 (t, 3H), 3.58 (br. s, 2H), 3.98 (q, 2H), 5.59 (d, 1H), 7.16 (d, 1H)

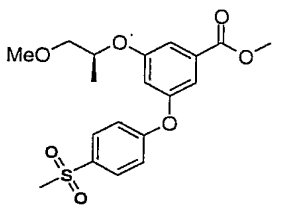
The required acids for Examples 11a-11h were prepared as described below:-

3-{(1S)-2-methoxy-(1-methylethyl)oxy}-5-{[4-(methylsulfonyl)phenyl]oxy}benzoic acid



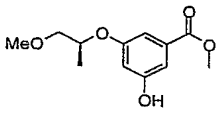
A solution of methyl 3-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-5-{[4-(methylsulfonyl)phenyl] oxy}benzoate (60.9 mmol) in THF (400 ml) was treated with a solution of 1M sodium hydroxide (125 mmol), and the reaction mixture stirred for 13 hours at ambient temperature. Most of the organic solvent was removed *in vacuo,* and the remaining solution was diluted with water (150 ml). The resulting aqueous solution was acidified to pH4 with 1M citric acid solution, and extracted with ethyl acetate (2 x 100 ml). The extracts were combined, washed with brine, dried ($MgSO_4$), and evaporated to give the desired compound (83% yield). ^{1}H NMR δ (d_6-DMSO): 1.2 (d, 3H), 3.2 (s, 3H), 3.26 (s, 3H), 3.44 (m, 2H), 4.63 (m, 1H), 7.05 (s, 1H), 7.11 (s, 1H), 7.2 (d, 2H), 7.3 (s, 1H), 7.9 (d, 2H); m/z 479 $(M-H)^-$

Methyl 3-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-5-{[4-(methylsulfonyl)phenyl]oxy} benzoate



A suspension of methyl 3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]benzoate (154 mmol), boronic acid (1.1 equivalents), copper (II) acetate (1.1 equivalents), triethylamine (5 equivalents) and freshly activated 4Å molecular sieves (200 g) in dichloromethane (500 ml) was stirred at ambient temperature and under ambient atmosphere for 2 days. The reaction mixture was filtered, the dichloromethane removed *in vacuo* and the residual oil partitioned between ethyl acetate and 1-2M hydrochloric acid. The ethyl acetate layer was separated, washed with aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica (with 20-60% ethyl acetate in isohexane as eluant) to give the desired ester (58% yield). ^{1}H NMR δ (d_6-DMSO): 1.2 (d, 3H), 3.2 (s, 3H), 3.26 (s, 3H), 3.44 (m, 2H), 3.8 (s, 3H), 4.65 (m, 1H), 7.05 (s, 1H), 7.11 (s, 1H), 7.2 (d, 2H), 7.3 (s, 1H), 7.9 (d, 2H)

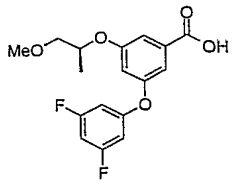
Methyl 3-Hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]benzoate



Methyl 3-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-5-{[phenylmethyl]oxy}benzoate (50.0g; 0.152mmol) was dissolved in a mixture of THF:ethanol (600ml) and the flask evacuated and purged with nitrogen (3 times). 10% Palladium on carbon (5.0g) was added and the flask further evacuated and finally purged with hydrogen gas. The reaction mixture was stirred at ambient temperature for 20 hours until completion. The reaction mixture was evacuated and purged with nitrogen (3 times). The catalyst was filtered off, and the filtrate concentrated *in vacuo* to give the desired compound (36.7g). ^{1}H NMR δ (d_6-DMSO): 1.2 (d, 3H), 3.25 (s, 3H), 3.44 (m, 2H), 3.82 (s, 3H), 4.55 (m, 1H), 6.6 (s, 1H), 6.9 (s, 1H), 6.95 (s, 1H), 9.8 (s, 1H)

The synthesis of methyl 3-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-5-{[phenylmethyl]oxy} benzoate is described above in Example 1.

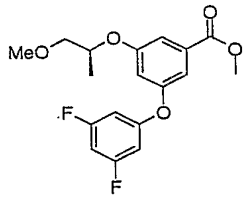
3-{(1S)-2-methoxy-(1-methylethyl)oxy}-5-{3,5-difluorophenoxy}benzoic acid



This was prepared from methyl 3-[(3,5-difluorophenyl)oxy]-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]benzoate using an analogous procedure to that described above for the synthesis of 3-{(1S)-2-methoxy-(1-methylethyl)oxy}-5-{[4-(methylsulfonyl)phenyl]oxy} benzoic acid:-

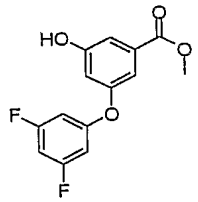
^{1}H NMR δ (d_6-DMSO): 1.21 (d, 3H), 3.26 (s, 3H obscured by solvent peak), 3.46 (m, 2H), 4.67 (m, 1H), 6.81 (d, 2H), 6.96 – 7.08 (m, 3H), 7.27 (s, 1H), 13.13 (bs, 1H); *m/z* 337 $(M-H)^-$

Methyl 3-[(3,5-difluorophenyl)oxyl-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]benzoate



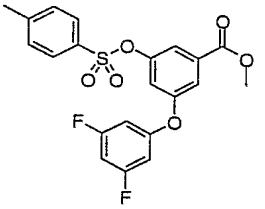
To a solution of methyl 3-[(3,5-difluorophenyl)oxy]-5-hydroxybenzoate (15.0 mmol), (*R*)-(-)-1-methoxy-2-propanol (18.75 mmol) and triphenylphosphine (18.0 mmol) in anhydrous THF (100 ml) at 0°C was added diisopropylazodicarboxylate (18.0 mmol). The reaction was stirred at ambient temperature overnight, concentrated *in vacuo,* and the residue triturated with a 1:1 mixture of ethyl acetate:isohexane. The solid was removed by filtration and the filtrate concentrated *in vacuo,* chromatographed on silica (using a Biotage Flash 75 eluting with 10-15% ethyl acetate in isohexane) to give the title compound (75% yield). ^{1}H NMR δ (d_6-DMSO): 1.21 (d, 3H), 3.27 (s, 3H obscured by solvent peak), 3.46 (m, 2H), 3.82 (s, 3H), 4.69 (m, 1H), 6.81 (dd, 2H), 7.01-7.07 (m, 2H), 7.10 (s, 1H), 7.28 (s, 1H)

Methyl 3-[(3,5-difluorophenyl)oxyl-5-hydroxybenzoate



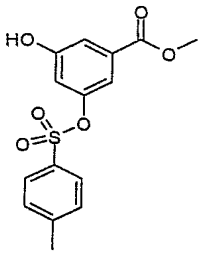
To a solution of methyl 3-[(3,5-difluorophenyl)oxy]-5-{[(4-methylphenyl)sulfonyl]oxy} benzoate (16.3 mmol) in methanol (60 ml) was added a 20% solution of potassium hydroxide in methanol (13.75 g). The mixture was heated at 50°C for 1 hour then allowed to cool. Water (20 ml) was added and the mixture immediately acidified with 1M hydrochloric acid. The methanol was removed *in vacuo* and the residue extracted with ethyl acetate. The organic phase was separated, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound (92% yield). ^{1}H NMR δ (d_6-DMSO): 3.80 (s, 3H), 6.72 (m, 1H), 6.79 (m, 2H), 6.98 – 7.05 (m, 2H), 7.19 (m, 1H), 10.18 (bs, 1H); *m/z* 279 $(M-H)^-$

Methyl 3-[(3,5-difluorophenyl)oxy]-5-{[(4-methylphenyl)sulfonyl]oxy}benzoate



To a solution of methyl 3-hydroxy-5-{[(4-methylphenyl)sulfonyl]oxy}benzoate (30 mmol), copper (II) acetate (36 mmol), 3,5-difluorophenylboronic acid (42 mmol) and 4Å molecular sieves (30 g) in dichloromethane (300 ml) was added triethylamine (150 mmol). The reaction was allowed to stir for 40 hours then filtered and concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with 1M citric acid solution, 1M sodium hydrogen carbonate solution and brine, then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica (Biotage Flash 75) eluting with 10- 25% ethyl acetate in isohexane to give the title compound (55% yield). ^{1}H NMR δ (d_6-DMSO): 2.39 (s, 3H), 3.83 (s, 3H), 6.74 (dd, 2H), 6.93 (m, 1H), 7.08 (m, 1H), 7.44 (m, 3H), 7.50 (s, 1H), 7.74 (d, 2H); *m/z* 452 $(M+NH_4)^+$, 433 $(M-H)^-$

Methyl 3-hydroxy-5-{[(4-methylphenyl)sulfonyl]oxy}benzoate

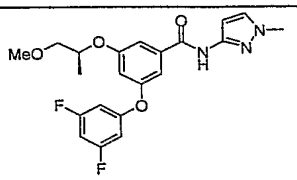
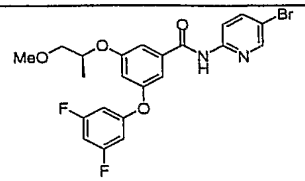


Methyl 3,5-dihydroxybenzoate (0.40g) and 4-toluenesulphonylchloride (0.45g) was stirred vigorously in diethyl ether (20ml) with saturated aqueous sodium hydrogen carbonate (20ml) at ambient temperature for 62 hours. The aqueous layer was removed and the residue washed sequentially with saturated aqueous sodium hydrogen carbonate, brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield a colourless oil. The crude product was dissolved in diethyl ether, washed with saturated aqueous potassium carbonate then with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a colourless oil which crystallised on standing to give the title compound (0.51g). ^{1}H NMR δ (d_6-DMSO): 2.43 (s, 3H), 3.82 (s, 3H), 6.66 (m, 1H), 6.97 (s, 1H), 7.26 (s, 1H), 7.47 (d, 2H), 7.75 (d, 2H); *m/z* 340 $(M+NH_4)^+$

Example 12: General Procedure for Amide Synthesis – Oxalyl Chloride Coupling

To a stirred solution of 3-{(1S)-2-methoxy-(1-methylethyl)oxy}-5-{3,5-difluorophenoxy} benzoic acid (0.285mmol) in dry dichloromethane (2ml), was added, dropwise under argon, oxalyl chloride (2 equivalents) and DMF (1 drop). The resulting solution was stirred at ambient temperature for 1-2 hrs. The solvent was removed *in vacuo* and the crude mixture taken up in pyridine (2ml) and added to the appropriate amine (2.2 equivalents). The reaction mixture was stirred at room temperature, or heated if necessary, and monitored by TLC and/or LCMS. The pyridine was removed *in vacuo,* and water and ethyl acetate added. The organic layer was washed sequentially with 1M citric acid and brine solution and dried ($MgSO_4$), concentrated *in vacuo,* and the residue chromatographed on silica (eluting with 30-90% ethyl acetate in isohexane) to give the desired product (typically 35-40% yield).

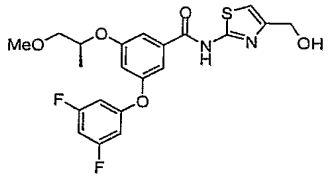
Examples 12a & 12b were prepared using the appropriate amine:

12a		419 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.23 (d, 3H), 3.27 (s, 3H obscured by solvent peak), 3.47 (m, 2H), 3.76 (s, 3H), 4.74 (m, 1H), 6.55 (d, 1H), 6.80 (d, 2H), 6.86 (m, 1H), 7.02 (m, 1H), 7.24 (s, 1H), 7.44 (s, 1H), 7.57 (s, 1H), 10.82 (br s, 1H)
12b[$]		493, 495 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.23 (d, 3H), 3.26 (s, 3H), 3.47 (m, 2H), 4.76 (m, 1H), 6.80 (dd, 2H), 6.92 (t, 1H), 7.02 (m, 1H), 7.26 (m, 1H), 7.45 (m, 1H), 8.04 (m, 1H), 8.13 (d, 1H), 8.49 (m, 1H), 11.01 (br s, 1H)

[$]In this example, the acid chloride was taken up in THF, followed by addition of pyridine and the appropriate amine.

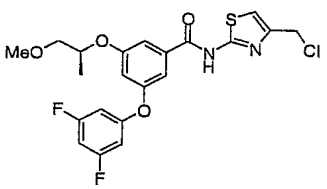
The synthesis of 3-{(1S)-2-methoxy-(1-methylethyl)oxy}-5-{3,5-difluorophenoxy}benzoic acid is described in Example 11 above.

Example 13: 3-(3,5-Difluorophenoxy)-N-[4-(hydroxymethyl)-1,3-thiazol-2-yl]-5-[2-(1S)-methoxy-(1-methylethyl)oxy]benzamide



To a solution of 3-(3,5-difluorophenoxy)-N-[4-chloromethyl-1,3-thiazol-2-yl]-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]benzamide (0.107 mmol) in THF (1 ml) was added 0.5M sodium hydroxide solution (1 ml). The reaction was stirred at ambient temperature for 2 hours and the organics removed *in vacuo*. The residue was acidified with 1M citric acid and partitioned between ethyl acetate and water. The organic phase was separated, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica eluting with 80% ethyl acetate in isohexane to give the title compound which was precipitated from a concentrated diethyl ether solution by the addition of isohexane to give a solid sample (35% yield). ^1H NMR δ (d_6-DMSO): 1.24 (d, 3H), 3.28 (s, 3H obscured by solvent peak), 3.48 (m, 2H), 4.49 (s, 2H), 4.75 (m, 1H), 6.83 (d, 2H), 6.93 (s, 1H), 6.98 (s, 1H), 7.04 (m, 1H), 7.32 (s, 1H), 7.54 (s, 1H); *m/z* 451 $(M+H)^+$, 449 $(M-H)^-$

3-(3,5-Difluorophenoxy)-N-[4-chloromethyl-1,3-thiazol-2-yl]-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]benzamide



To a stirred solution of 3-{(1S)-2-methoxy-(1-methylethyl)oxy}-5-{3,5-difluorophenoxy}benzoic acid (3.06mmol) in dichloromethane (20ml) was added 3 drops of DMF and oxalyl chloride (6.12mmol; 2.0 equivalents) dropwise, and the resulting mixture

stirred at ambient temperature for 5 hours. The reaction mixture was concentrated *in vacuo*, azeotroped with toluene and dried overnight at reduced pressure. The residue was dissolved in dichloromethane and 4-chloromethylthiazol-2-ylamine (3.36mmol), triethylamine (3.36mmol) and dimethylaminopyridine (0.31mmol) added. The resulting mixture was stirred for 16 hours at ambient temperature. The reaction mixture was washed sequentially with 2M hydrochloric acid and 1M sodium hydrogencarbonate solution, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed (eluting with 15-20% ethyl acetate in isohexane) to give the desired compound (33% yield). ^{1}H NMR δ (d_6-DMSO): 1.24 (d, 3H), 3.28 (s, 3H obscured by solvent peak), 3.49 (m, 2H), 4.76 (m, 3H), 6.84 (dd, 2H), 6.94 (s, 1H), 7.04 (m, 1H), 7.32 (m, 2H), 7.55 (s, 1H), 12.77 (bs, 1H); m/z 469, 471 $(M+H)^+$, 467, 469 $(M-H)^-$

The synthesis of 3-{(1S)-2-methoxy-(1-methylethyl)oxy}-5-{3,5-difluorophenoxy}benzoic acid is described in Example 11 above.

BIOLOGICAL

Tests:

The biological effects of the compounds of formula (I) may be tested in the following way:

(1) Enzymatic activity of GLK may be measured by incubating GLK, ATP and glucose. The rate of product formation may be determined by coupling the assay to a G-6-P dehydrogenase, NADP/NADPH system and measuring the increase in optical density at 340nm (Matschinsky et al 1993).

(2) A GLK/GLKRP binding assay for measuring the binding interactions between GLK and GLKRP. The method may be used to identify compounds which modulate GLK by modulating the interaction between GLK and GLKRP. GLKRP and GLK are incubated with an inhibitory concentration of F-6-P, optionally in the presence of test compound, and the extent of interaction between GLK and GLKRP is measured. Compounds which either displace F-6-P or in some other way reduce the GLK/GLKRP interaction will be detected by a decrease in the amount of GLK/GLKRP complex formed. Compounds which promote F-6-P binding or in some other way enhance the GLK/GLKRP interaction will be detected by an

increase in the amount of GLK/GLKRP complex formed. A specific example of such a binding assay is described below

GLK/GLKRP scintillation proximity assay

Recombinant human GLK and GLKRP were used to develop a "mix and measure" 96 well SPA (scintillation proximity assay) as described in WO01/20327 (the contents of which are incorporated herein by reference). GLK (Biotinylated) and GLKRP are incubated with streptavidin linked SPA beads (Amersham) in the presence of an inhibitory concentration of radiolabelled [3H]F-6-P (Amersham Custom Synthesis TRQ8689), giving a signal. Compounds which either displace the F-6-P or in some other way disrupt the GLK / GLKRP binding interaction will cause this signal to be lost.

Binding assays were performed at room temperature for 2 hours. The reaction mixtures contained 50mM Tris-HCl (pH 7.5), 2mM ATP, 5mM $MgCl_2$, 0.5mM DTT, recombinant biotinylated GLK (0.1 mg), recombinant GLKRP (0.1 mg), 0.05mCi [3H] F-6-P (Amersham) to give a final volume of 100ml. Following incubation, the extent of GLK/GLKRP complex formation was determined by addition of 0.1mg/well avidin linked SPA beads (Amersham) and scintillation counting on a Packard TopCount NXT.

(3) A F-6-P / GLKRP binding assay for measuring the binding interaction between GLKRP and F-6-P. This method may be used to provide further information on the mechanism of action of the compounds. Compounds identified in the GLK/GLKRP binding assay may modulate the interaction of GLK and GLKRP either by displacing F-6-P or by modifying the GLK/GLKRP interaction in some other way. For example, protein-protein interactions are generally known to occur by interactions through multiple binding sites. It is thus possible that a compound which modifies the interaction between GLK and GLKRP could act by binding to one or more of several different binding sites.

The F-6-P / GLKRP binding assay identifies only those compounds which modulate the interaction of GLK and GLKRP by displacing F-6-P from its binding site on GLKRP.

GLKRP is incubated with test compound and an inhibitory concentration of F-6-P, in the absence of GLK, and the extent of interaction between F-6-P and GLKRP is measured. Compounds which displace the binding of F-6-P to GLKRP may be detected by a change in the amount of GLKRP/F-6-P complex formed. A specific example of such a binding assay is described below

F-6-P / GLKRP scintillation proximity assay

Recombinant human GLKRP was used to develop a "mix and measure" 96 well scintillation proximity assay) as described in WO01/20327 (the contents of which are incorporated herein by reference). FLAG-tagged GLKRP is incubated with protein A coated SPA beads (Amersham) and an anti-FLAG antibody in the presence of an inhibitory concentration of radiolabelled [3H]F-6-P. A signal is generated. Compounds which displace the F-6-P will cause this signal to be lost. A combination of this assay and the GLK/GLKRP binding assay will allow the observer to identify compounds which disrupt the GLK/GLKRP binding interaction by displacing F-6-P.

Binding assays were performed at room temperature for 2 hours. The reaction mixtures contained 50mM Tris-HCl (pH 7.5), 2mM ATP, 5mM $MgCl_2$, 0.5mM DTT, recombinant FLAG tagged GLKRP (0.1 mg), Anti-Flag M2 Antibody (0.2mg) (IBI Kodak), 0.05mCi [3H] F-6-P (Amersham) to give a final volume of 100ml. Following incubation, the extent of F-6-P/GLKRP complex formation was determined by addition of 0.1mg/well protein A linked SPA beads (Amersham) and scintillation counting on a Packard TopCount NXT.

Production of recombinant GLK and GLKRP:

Preparation of mRNA

Human liver total mRNA was prepared by polytron homogenisation in 4M guanidine isothiocyanate, 2.5mM citrate, 0.5% Sarkosyl, 100mM b-mercaptoethanol, followed by centrifugation through 5.7M CsCl, 25mM sodium acetate at 135,000g (max) as described in Sambrook J, Fritsch EF & Maniatis T, 1989.

Poly A^+ mRNA was prepared directly using a FastTrack™ mRNA isolation kit (Invitrogen).

PCR amplification of GLK and GLKRP cDNA sequences

Human GLK and GLKRP cDNA was obtained by PCR from human hepatic mRNA using established techniques described in Sambrook, Fritsch & Maniatis, 1989. PCR primers were designed according to the GLK and GLKRP cDNA sequences shown in Tanizawa et al 1991 and Bonthron, D.T. *et al* 1994 (later corrected in Warner, J.P. 1995).

Cloning in Bluescript II vectors

GLK and GLKRP cDNA was cloned in E. coli using pBluescript II, (Short et al 1998) a recombinant cloning vector system similar to that employed by Yanisch-Perron C *et al* (1985), comprising a colEI-based replicon bearing a polylinker DNA fragment containing multiple unique restriction sites, flanked by bacteriophage T3 and T7 promoter sequences; a filamentous phage origin of replication and an ampicillin drug resistance marker gene.

Transformations

E. Coli transformations were generally carried out by electroporation. 400 ml cultures of strains DH5a or BL21(DE3) were grown in L-broth to an OD 600 of 0.5 and harvested by centrifugation at 2,000g. The cells were washed twice in ice-cold deionised water, resuspended in 1ml 10% glycerol and stored in aliquots at -70^{0}C. Ligation mixes were desalted using Millipore V series™ membranes (0.0025mm) pore size). 40ml of cells were incubated with 1ml of ligation mix or plasmid DNA on ice for 10 minutes in 0.2cm electroporation cuvettes, and then pulsed using a Gene Pulser™ apparatus (BioRad) at 0.5kVcm^{-1}, 250mF. Transformants were selected on L-agar supplemented with tetracyline at 10mg/ml or ampicillin at 100mg/ml.

Expression

GLK was expressed from the vector pTB375NBSE in E.coli BL21 cells,, producing a recombinant protein containing a 6-His tag immediately adjacent to the N-terminal methionine. Alternatively, another suitable vector is pET21(+)DNA, Novagen, Cat number 697703. The 6-His tag was used to allow purification of the recombinant protein on a column packed with nickel-nitrilotriacetic acid agarose purchased from Qiagen (cat no 30250).

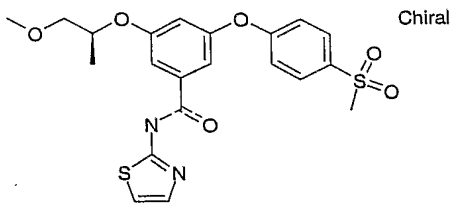
GLKRP was expressed from the vector pFLAG CTC (IBI Kodak) in E.coli BL21 cells, producing a recombinant protein containing a C-terminal FLAG tag. The protein was purified initially by DEAE Sepharose ion exchange followed by utilisation of the FLAG tag for final purification on an M2 anti-FLAG immunoaffinity column purchased from Sigma-Aldrich (cat no. A1205).

Biotinylation of GLK:

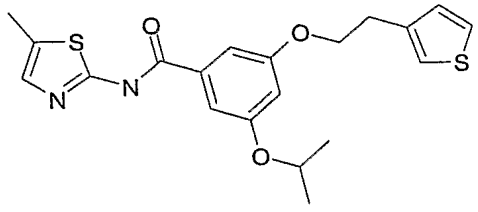
GLK was biotinylated by reaction with biotinamidocaproate N-hydroxysuccinimide ester (biotin-NHS) purchased from Sigma-Aldrich (cat no. B2643). Briefly, free amino groups of the target protein (GLK) are reacted with biotin-NHS at a defined molar ratio forming stable amide bonds resulting in a product containing covalently bound biotin. Excess, non-conjugated biotin-NHS is removed from the product by dialysis. Specifically, 7.5mg of GLK was added to 0.31mg of biotin-NHS in 4mL of 25mM HEPES pH7.3, 0.15M KCl, 1mM dithiothreitol, 1mM EDTA, 1mM $MgCl_2$ (buffer A). This reaction mixture was dialysed against 100mL of buffer A containing a further 22mg of biotin-NHS. After 4hours excess biotin-NHS was removed by extensive dialysis against buffer A.

Oral Glucose Tolerance Test (OGTT)

Oral glucose tolerance tests were done on conscious Zucker obese fa/fa rats (age 12-13 weeks or older) fed a high fat diet (45 % kcal fat) for at least two weeks prior to experimentation. The animals were fasted for 2 hours before use for experiments. A test compound or a vehicle was given orally 120 minutes before oral administration of a glucose solution at a dose of 2 g/kg body weight. Blood glucose levels were measured using a Accucheck glucometer from tail bled samples taken at different time points before and after administration of glucose (time course of 60 minutes). A time curve of the blood glucose levels was generated and the area-under-the-curve (AUC) for 120 minutes was calculated (the time of glucose administration being time zero). Percent inhibition was determined using the AUC in the vehicle-control group as zero percent inhibition.



Example 11b



Example II107

Compounds of the invention generally have an activating activity for glucokinase with an EC_{50} of less than about 500nM. For example, Example 11b has an EC_{50} of 30nM.

Example 11b and Example II107 in WO 03/015774 have broadly similar EC_{50} values. However Example 11b has superior oral exposure and exhibits 29% OGTT activity at 10 mg/kg but Example II107 in WO 03/015774 is not active at 10 mg/kg.

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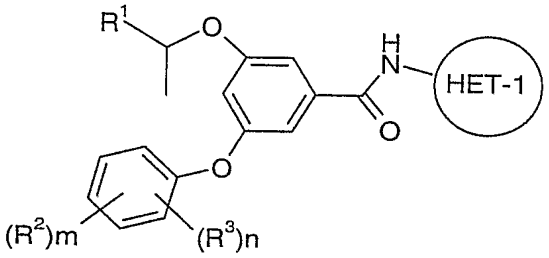
Claims:

1. A compound of Formula (I):



(I)

wherein:

R^1 is methoxymethyl;

R^2 is selected from $-C(O)NR^4R^5$, $-SO_2NR^4R^5$, $-S(O)_pR^4$ and HET-2;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^6;

HET-2 is a 4-, 5- or 6-membered, C- or N-linked heterocyclyl ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- , and wherein a sulphur atom in the heterocyclic ring may optionally be oxidised to an S(O) or $S(O)_2$ group, which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^7;

R^3 is selected from halo, fluoromethyl, difluoromethyl, trifluoromethyl, methyl, methoxy and cyano;

R^4 is selected from hydrogen, (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$] and HET-2;

R^5 is hydrogen or (1-4C)alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached may form a 4-6 membered heterocyclyl ring system as defined by HET-3;

R^6 is independently selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl and HET-4;

R^7 is selected from $-OR^5$, (1-4C)alkyl, -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-3 is an N-linked, 4 to 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to an S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8;

R^8 is selected from $-OR^5$, (1-4C)alkyl, -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkylamino, di(1-4C)alkylamino, HET-3 (wherein said ring is unsubstituted), (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-4 is a 5- or 6-membered, C-or N- linked unsubstituted heteroaryl ring containing 1, 2 or 3 ring heteroatoms independently selected from O, N and S;

p is (independently at each occurrence) 0, 1 or 2;

m is 0 or 1;

n is 0, 1 or 2;

provided that when m is 0, then n is 1 or 2;

or a salt, pro-drug or solvate thereof.

2. A compound of the formula (I) as claimed in Claim 1 wherein R^1 has the (S) configuration.

3. A compound of the formula (I) as claimed in Claim 1 or Claim 2, or a salt, pro-drug or solvate thereof, wherein HET-1 is a 5-membered ring.

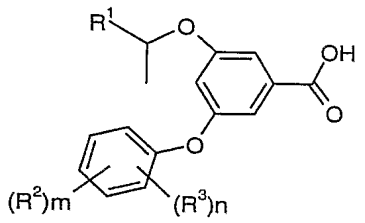
4. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 3, or a salt, pro-drug or solvate thereof, together with a pharmaceutically acceptable diluent or carrier.

5. A compound according to any one of Claims 1 to 3 for use in the preparation of a medicament for treatment of a disease mediated through GLK.

6. A method of treating GLK mediated diseases by administering an effective amount of a compound of Formula (I) as claimed in any one of Claims 1 to 3or salt, solvate or pro-drug thereof, to a mammal in need of such treatment.

7. A process for the preparation of a compound of Formula (I) as claimed in any one of Claims 1 to 3, which comprises (wherein variables are as defined in Claim 1 unless otherwise stated):

(a) reaction of an acid of Formula (III) or activated derivative thereof with a compound of Formula (IV),

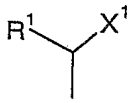


(III)

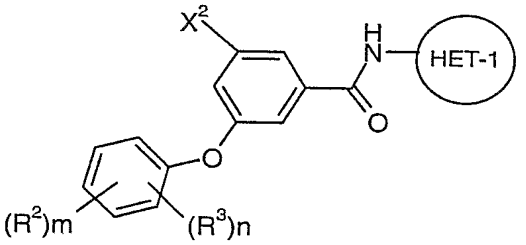
(IV);

or

(b) reaction of a compound of Formula (V) with a compound of Formula (VI),



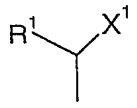
(V)



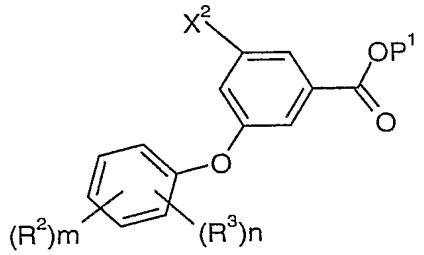
(VI)

wherein X^1 is a leaving group and X^2 is a hydroxyl group or X^1 is a hydroxyl group and X^2 is a leaving group;

[or by reaction with the intermediate ester Formula (VII), wherein P^1 is a protecting group followed by ester hydrolysis and amide formation];



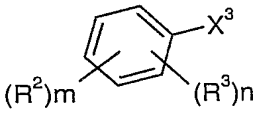
(V)



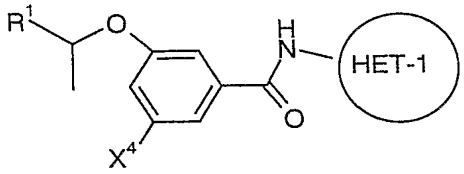
(VII)

or

(c) reaction of a compound of Formula (VIII) with a compound of Formula (IX)



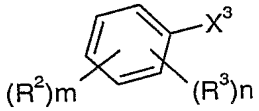
(VIII)



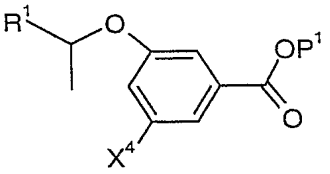
(IX)

wherein X^3 is a leaving group or an organometallic reagent and X^4 is a hydroxyl group or X^3 is a hydroxyl group and X^4 is a leaving group or an organometallic reagent;

[or by reaction or (VIII) with the intermediate ester Formula (X), followed by ester hydrolysis and amide formation];



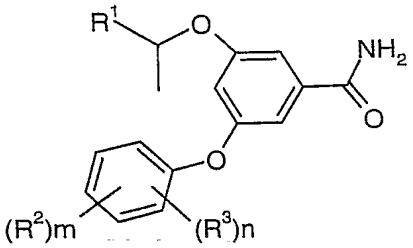
(VIII)



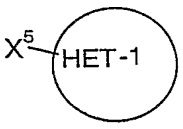
(X)

or

(d) reaction of a compound of Formula (XI) with a compound of Formula (XII),



(XI)



(XII);

wherein X^5 is a leaving group;

and thereafter, if necessary:

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups; and/or

iii) forming a salt, pro-drug or solvate.